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Smoke Investigation   Bulletin No. 9

Papers on the Influence of Smoke on Health

Edited by

Oskar Klotz and Wm. Charles White

Mellon Institute of Industrial Research and School of Specific Industries

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University of Pittsburgh
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Table of Contents

Introduction

The present bulletin contains the papers representing the work done by the physicians and laboratory investigators on the Staff of the Smoke Investigation.

Much difficulty was experienced by the physicians in arriving at definite conclusions, because the present state of our knowledge does not admit of satisfying and positive pronouncements of the relation of smoke to diseases of the eye, ear, nose and throat and other diseases requiring surgical intervention. The psycological aspects of the problem have been discussed by J. E. W. Wallin, Ph. D. in Bulletin No. 3 of this series.

Doctor Cohoe has prepared his resume of the literature especially for this bulletin. The papers of Doctors Klotz, Holman, Haythorn and White have all been published or read elsewhere in scientific circles.

Doctor Cohoe's paper gives a review of the history of the thoughts and work of men leading up to our present knowledge and attempts no decision of the vexed problems.

The work undertaken by Doctor Klotz deals with the gross pathological changes which arise from the excessive inhalation of a carbon-laden air. Whereas the presence of small quantities of smoke has no harmful effect upon the tissues, it is shown that the continuous accumulation of carbon may act quite differently. This feature alone in our problem deserves further attention.

The work of Doctors Haythorn and Holman are both very valuable contributions to this subject, containing the results of original research that aid greatly our search after the truth of the relation of smoke to health. Doctor Haythorn's paper brings out some suggestive points in indicating the histological changes induced by smoke and their relation to pneumonia.

It will be seen in reading all of these papers that practically all investigators whose opinions are based on

grounds other than theory, are agreed that smoke has a tremendous influence in increasing the incident severity and mortality of acute diseases of the air passages. It would appear that this increased susceptibility is, in part, the result of the lowering of our natural body resistance. In simple terms, the smokier the atmosphere, the more the colds and bronchitis, and the more money paid to doctors.

On the other hand, the relation of smoke to tuberculosis is one of greatly divided opinion and the burden of proof is that if smoke has any influence at all, it is not a harmful one. The work of Doctor Klotz and of Doctor Haythorn offers some explanation of this probability. If this be the truth and tuberculosis is not influenced by smoky atmosphere, it is time to stop the utterance of this popular fallacy which can do naught other than harm in sacrificing the confidence of the public in those who should guide them.

We feel very sure that a careful perusal of this bulletin will fully repay every reader of it.

WM. CHARLES WHITE.

The Relation of Atmospheric Smoke and Health

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INTRODUCTION.

In the present paper an attempt has been made to cull from scientific literature the evidence, pro and con, which has been adduced by various scientists whose opinions would seem to merit consideration, concerning the role played by a smoke-laden atmosphere upon the bodily health of the community.

Thanks to the triumphs of the modern science of sanitation, a successful assault has been waged against such water-borne diseases as typhoid fever and cholera by a close surveillance of the water supply and sewage disposal within our cities, while, more recently, the efforts of the Public Health Bureau have rendered it possible for our citizens to obtain pure food stuffs, free from adulteration. Meanwhile, strangely enough, the problem of pure air has received but scanty consideration.

This omission appears the more astounding when regarded in the light of a fact stated by Cohen that every man and woman breathes about two thousand gallons of air in twenty-four hours, or about thirty-four pounds in weight, as contrasted with a daily intake of five and one-half pounds of liquid and solid foods. Or, in other words, the weight of the air inhaled daily is more than six times the weight of the daily consumption of food.

Fortunately, within recent years, largely owing to the organization of Smoke Abatement Leagues, an agitation has been begun advocating an examination of the air in a manner comparable to the careful scrutiny now required for our water and food supplies and of the sewage disposal.

In a survey of the various factors which tend to con-
taminate the atmosphere of cities, smoke is conceded by
all to be the greatest source of pollution. The Smoke
Abatement Leagues, in their efforts to purge the air of
this menace, have encountered numerous obstacles, nota-
bly an apathetic public and a certain antagonism on the
part of manufacturers against any attempt to curtail the
amount of industrial smoke. The lethargy of the public
in regard to the smoke evil doubtless has arisen from the
circumstance that, until recently, the opinion has pre-
vailed in the minds of the laity, and indeed of physicians
as well, that a smoky atmosphere is not only not injurious
but at times even beneficial to the public health. This
supposition gained favor from an observation, largely er-
roneous, that coal miners are not prone to contract tuber-
culosis.

A belief in the antiseptic qualities of smoke has been
entertained by many physicians for several centuries. It
is a matter of historical interest that during the Plague
Year in London fires were kept burning in the hope of sup-
pressing the epidemic for "it was alleged that the sul-
phurous and nitrous particles that are often found to be
in the coal, with the bituminous substance which burns,
are all assisting to clear and purge the air and render it
wholesome and safe to breathe in."

Quite apart from any mooted question as to the ulti-
mate effect on health, the citizens of Pittsburgh have, for
many decades, been keenly alive to the bodily discomfort
resulting from the omnipresent smoke pall in the com-
munity. As early as 1804, General Neville, the then Bur-
gess of Pittsburgh, is quoted (O'Connor) as having stated
with reference to the smoke nuisance "that not only the
comfort, health, and in some measure, the consequence
of the place, the peace and harmony of the inhabitants,
depend upon speedy measures being adopted to remedy
the nuisance." Nor, indeed, were visitors, then as now,
slow to observe the baneful influence of the smoke upon
the inhabitants for, in 1818, Eswick Evans wrote that
"'owing to the exclusive use of coal here, both by the man-

ufacturers and by private families, the whole town presents a smoky appearance. Even the complexion of the people is affected by this cause." Major Forman noted in 1797 that "the coal smoke is such as to affect the skin of the inhabitants." Another writer of note who corroborated these observations was Henry Bradshaw Fearon, a London surgeon, who, in 1817, remarked of Pittsburgh that "the smoke is extreme, giving to the town and its inhabitants a very sombre aspect."

Such casual observations, extending over a period of more than a century, only serve to emphasize a deplorable degree of apathy on the part of the citizens in tolerating a nuisance whose injurious effects have been so long and so clearly proclaimed. Yet Pittsburgh fares no more ill than many of the large industrial centers of the world with respect to the smoke evil.

In the present resume of the literature, the aim has been to present an analysis of the vital statistics, special investigations, and experimentations bearing upon the problem of the relation of smoke and health, and no attempt has been made to deduce other than a few generalizations concerning local conditions in Pittsburgh. A special study of the local conditions and vital statistics from a viewpoint of the status of smoke as a possible factor in increasing the local death rate has been reserved for another bulletin of the present series.

I.

EVIDENCE FAVORABLE TOWARDS SMOKE.

In a general survey of the literature concerning the role of smoke in the causation of disease, it is not surprising that an expression of doubt concerning the harmfulness of smoke in the community should be encountered in certain quarters, nor, indeed, that certain scientists should entertain a sentiment favorable towards smoke. While the smoky atmosphere of an industrial center continues to be the index of the prosperity of the town, the community is likely to overlook the discomfort and danger of the same and foster any attempt to defend its antiseptic qualities. In an impartial weighing of the evidence, pro and con, regarding smoke such favorable opinions, coming from observers whose authority cannot be overlooked, merit consideration.

The popular idea that smoke does not act injuriously on health, but only uncomfortably, has served to retard in no small measure the work of smoke abatement. Our standard works on hygiene take little or no cognizance of the harmful effects of smoke. Many authors, who do not regard smoke as injurious, attempt to establish their claim by a citation of the low death rates of certain industrial towns. At the Manchester meeting of the Smoke Abatement League of Great Britain, 1911, a delegate made the assertion that his town (Coatbridge, a smoky industrial town) was one of the healthiest of towns, admitting, however, that the smoke was at times very annoying. The reason for his defense was obvious in his statement that "furnaces did make smoke and to prohibit the making of smoke would prohibit the making of puddled iron." A writer in the Revue Industrielle (November, 1899) voices the same sentiment in stating: "In spite of the abundance of smoke, people are no worse off in Leeds than elsewhere.

Facades of houses are soiled but the inhabitants do not suffer. Are we going to learn one of these days that smoke, thanks to its antiseptic properties, contributes to making the atmosphere healthful?"

The medical profession, indeed, has at times given utterances to similar opinions. At a conference held in the Franklin Institute, Philadelphia, a few years ago a physician is quoted as saying: "I do not mean to intimate that the smoke nuisance injures health in any ordinary sense; on the contrary, I am inclined to think that the essence of this, which is always a minute amount of free carbon in the air, is rather healthful than otherwise." Similarly, following a discussion of the smoke evil at a meeting of the Philadelphia County Medical Society, 1906, it was recorded, "that the nose, throat and eyes are directly injured by smoke was admitted beyond a doubt, but whether the presence of soot in the human lungs is an indifferent matter, or an injury, was left undecided. There is little evidence to show that the presence of smoke in the air increases the morbidity or the mortality of the community."

In a study of anthracosis as a factor in the causation of lung diseases, Trotter has commented upon the rarity of pulmonary tuberculosis among miners, and from his observations he was lead to regard coal dust as productive of little, if any, harm to the organism. His conclusions would seem to show that coal dust renders miners more or less immune to tuberculosis.

1. Coal dust may remain imbedded under the skin for years without producing any irritation whatever.

2. The death returns from phthisis in a colliery district show a greater proportion of deaths among females than males.

3. Colliery surgeons almost invariably state that phthisis is not so common in mining as in other districts.

4. In the majority of phthisis cases which do occur, there is a strong family history on one or both sides.

So popular has been this fancy that coal dust acts beneficially in pulmonary tuberculosis that it has been for years a common custom for persons affected with this disease to resort to coal mines, or to build fires and inhale the smoke, hoping thereby to affect a cure, on the quasi-scientific supposition that the inhaled carbon promoted healing. As will be shown later, more careful recent investigation has demonstrated the fallacy of this supposition and has placed a revised interpretation on the apparent low death rate of miners from tuberculosis.

II.

EVIDENCE OF A DOUBTFUL NATURE.

In a second grouping can be assembled the opinions of a number of scientists who, while they would be constrained to regard smoke as a cause of ill health, yet in a spirit of scientific conservatism consider the case as not proven. The study of the problem of the effect of smoke upon health presents many complicating factors, which render judgment difficult.

Among these, Mehl states that "no one has yet shown that smoke and fog are injurious to health," but the same writer proceeds to demonstrate by means of statistics that the increased death rate from respiratory diseases, in large industrial centers, must be referred to the influence of smoke and dust. Cohen, one of the most active workers in the crusade against industrial smoke, while realizing that it is quite true that pulmonary disease is much higher in towns than in the country, concedes that "we cannot single out smoke as the cause, because the problem is complicated by so many other factors."

Another writer, Glinzer, while regarding smoke as truly injurious to health in a degree not as yet determined, appreciates its twofold qualities. Smoke, he believes, possesses excellent germicidal and disinfecting properties. "Obnoxious vapors and other harmful products carried by the air are absorbed and retained by the material elements of smoke, and are finally carried away harmlessly by the rain, so that smoke, on the contrary, can be stamped as a purifier of the atmosphere and a benefactor of the human race. In my opinion, this is doubtless true; it is only a question of which influence is the stronger. I believe we can safely depend on our instinct, and this tells us decidedly that smoke does not agree with us."

Another careful investigator who regards the proof as incomplete is Rubner. He believes that while there can be scarcely any doubt of the possibility, perhaps even the probability, that the smoke content of the air is an important element of injury to health; a matter of the coincidence of bad air and disease is another matter. "Such a proof can scarcely be attained even by the standard of very exact etiological investigations. If there is an entire lack of knowledge as to how the pollution of the air by smoke is distributed in the country in general, and as to whether the regions with impure air coincide to some extent with those of more frequent lung diseases, there is still further lack of proof as to whether the condition of the air is alone responsible for the injury, or whether the remaining within doors does not also contribute to it. The injuries resulting from a pollution of the air might also be traced to climatic influences."

III.

EVIDENCE OF A POSITIVE NATURE.

Passing over the foregoing evidence, which is more or less equivocal in kind, we come to the evidence of a more positive nature, which has been gleaned from the many monographs appearing in the literature dealing with the smoke problem, in which the authors have attempted to establish proof concerning the pernicious influence of smoke and its constituents upon the individual and public health. In this connection, the significant fact is revealed that the more exhaustive the investigations undertaken by the various scientists, from the viewpoint of sanitation, vital statistics, and animal experimentation, by so much the more do the conclusions evolved attest the deleterious effect of smoke on health. Such observations have been made from many angles—the effect of smoke as a whole, and the effect of its various ingredients, as well as what may be regarded as the direct primary effect together with the more remote secondary effects of a smoke-laden atmosphere. Dealing first, therefore, with the opinions promulgated as to the general effect of smoke, or the influence of smoke as a composite entity upon the health of the community, we shall pass to the evidence obtained as to the effect of the various constituents of smoke, such as carbon, soot, and gaseous elements upon the human organism, and finally, to the indirect effects of smoke in impairing the health of a community.

(A) THE EFFECTS OF SMOKE AS A WHOLE.

The general effects of a smoky atmosphere upon the health of inhabitants have been broadly summarized by Wainwright, who states that smoke interferes with the welfare of a community—

1.   By conducing to the formation of fog and rain.

2. By shutting out sunlight and depriving us of certain qualities of light of great importance in regard to changes in organic matter.

3. By depositing soot and rendering houses or their contents dirty.

Moreover, with respect to the individual he believes the acid content of smoke and the irritating particles suspended in it are harmful to the tissues of the nose, throat and eyes, and especially the lungs and air passages whether these be in a healthy or other condition. He further indicts smoke as a menace indirectly to the sick of a community, averring that "it aggravates to the discomfort of those suffering from all forms of heart trouble; increases the distress of those who have nervous complaints; lowers the tone of general health; is a peril to the aged; diminishes buoyancy of spirit as well as reducing still further an already lowered resistance to disease."

Valuable evidence has been presented by a number of Medical Health Officers of smoky industrial cities concerning prevailing health conditions. This is especially true of the city of Manchester which may well be selected as a type of smoky towns. Concerning local conditions in the city, Dr. Niven, M.H.O., has written: "Manchester is still conspicuous for its high mortality, and it is especially conspicuous for its excessive death rate from phthisis, pneumonia, bronchitis, and heart disease. All forms of septic disease are unduly prevalent. The windows of houses and factories are closed on account of the dirt which enters by the open window. Less attention is paid to cleanliness than is needful for health. Fresh air is needed not only in the treatment of consumption, but is equally necessary for the raising of healthy children. * * * There has been a great advance in the physical well-being of the population, but the death rate is still among the highest prevailing in great towns. Manchester, like other towns, exhibits an immense improvement as regards some diseases, more especially smallpox, enteric fever, and scarlet fever. * * * The mouth breather is at a much greater disadvantage in Manchester

and the large towns than he is in the country and it is important that adenoids should be attended to."

The report of Dr. Tatham, M.H.O., in 1890, speaks even yet more strongly of the local conditions in Manchester. This writer states that the working life of the people in central Manchester is curtailed by ten years. To quote from his report: "Our people lose 30% of their lives. * * * The acids of smoke and carbon particles operate upon the lungs for years before they finally destroy them."

If the criterion of physical fitness for army service may be taken as an index of the health of the citizens of a smoky city, the statistics for Manchester, according to Horsfall, reveal an appalling condition. This author writes: "In Manchester in 1899 of 11,000 men who wanted to enlist only 9% were found to be physically fit for the regiments of the line, and at the present moment the Navy could only accept 14% of the boys belonging to all grades of society who wanted to join. There are no figures among races of the world comparable with these in their revelation of physical deterioration."

Among the numerous investigations which have been undertaken to determine the direct effect of smoke as a source of ill health, it is not surprising to find that the burden of proof has been sought in the relation of smoke to diseases of the respiratory organs, since the lung tissue is necessarily first invaded by the smoke content of the air inhaled. Accordingly, the majority of observers have based their studies upon the incidence of lung disease in smoky industrial cities. While vital statistics may not furnish, perhaps, the ideal criterion of the health of a community, they afford without doubt the most readily available standard of comparison.

In reference to the irritating effect upon the lung tissue of the constant breathing of a smoky atmosphere, Reed writes: "The slight morning cough with the equally slight expectoration of black mucus is an experience familiar to denizens of a smoky town, but an experience which, to the medical mind, suggests a persistent although

slight irritation of the upper air passages that are thus
made hospital avenues for tuberculous infection."

Supfle, another observer, corroborates the opinion of
the former writer in saying: "Climate has much to do
with the effects of smoke on health. Southern cities, with
warm climate, do not suffer so much as those in the north.
Cities lying in the valleys suffer most. The acids given
off in fumes provoke a hypersecretion of the mucous
glands of the trachea and bronchi. In time, one accommo-
dates oneself to the new conditions and one apparently
feels well. And herein lies the great danger, as one
ceases to cough and outward symptoms no longer appear,
the injurious effects remain."

According to statistics cited by Wainwright, the death
rate from diseases of the respiratory organs in Manchester
was in 1874, 7.7, and in 1893, 23.2 per 1,000 of deaths from
all causes; and in Westmoreland, England, the death rate
from the same diseases was but 2.29 in 1888, and 13.7
in 1893. These increased death rates he charges to an in-
creased consumption of coal and consequent smoke.

Russell has utilized the following comparative table
to show the extreme frequency of death due to lung dis-
eases occurring in and about the smoky atmosphere of
Glasgow in the year 1880:

	Contagious Diseases	Lung Diseases	Other Diseases	Total
Rural Districts	289	354	996	1,639
City of Glasgow	773	1,024	1,232	3,029
Thinly populated part of Glasgow (36 persons per acre)	450	600	870	1,920
Densely populated part of Glasgow (512 persons per acre)	1,020	1,860	1,600	4,480

Similarly, a table compiled for Manchester reveals a
strikingly high incidence of deaths from respiratory dis-
eases. The death rate in different parts of Manchester

per 100,000 for the year ending the third quarter of 1891 was as follows:

	Contagious Diseases	Lung Diseases	Other Diseases	Total
Thinly populated part	241	534	954	1,729
Densely populated part	510	1,544	1,798	3,752

Concerning southeast Lancashire, a smoky industrial center, Dr. Brown states that the death rate in that district from respiratory diseases is very considerably higher than in the southern and western parts of the country.

Far and away the most comprehensive study of the direct effect of smoke upon the respiratory organs has been made by Dr. Louis Ascher of Konigsberg. He has published several monographs dealing with the subject both from the standpoint of vital statistics and animal experimentation. His conclusions, while not universally accepted, have been drawn from the most careful scientific investigation of the problem of smoke and health yet presented. His work merits more than a passing survey.

In pursuing his observations, Ascher utilized the statistics of the Imperial Health Bureau of the German Empire. Respiratory diseases he separated into two main groups, the tuberculous (designated T) and the non-tuberculous (NT). In some instances the German statistics were compared with those of other countries, as England and America. A study of these statistics, dating back to 1875, lead him to conclude that since 1875 there has been an increase in acute inflammatory diseases of the respiratory organs. The possible bearing of a diminished power of resistance, or of climatic or infectious causes, as contributing to this increase was considered by the author, but each of these in turn were found not to be a factor in the increase of acute lung diseases. Was this increase confined to Prussia during this period? An examination of the mortality tables gave a negative answer and revealed a similar increase in the whole of Germany, as well as in England and America. In the latter countries he found

an increase in the death rate from pneumonia between 1890-1900 of 186.9 to 192 of every 100,000 of the population. He made a study of conditions in agricultural districts where he found a lowering of the death rate from tuberculosis and a rise in acute lung diseases. His conclusion from his earlier statistical studies was as follows: "The increase in the mortality of acute lung diseases must be the result of some harmful factor which, it is true, is found in agricultural communities, but with a much higher increase in industrial centers. This factor is not limited to the places of industrial work but is also found in the homes, as proven by the mortality tables for infants and old people. The cause of this increase can only be the smoke of the coal fires."

Ascher was fully cognizant of the opposition that such conclusions might engender on the part of the critics. The lethargy of the public in regard to the smoke problem has been due, he believes, to the fact that smoke has not been considered harmful. The reasons why smoke has not been regarded as a menace he summarizes as follows: (1) Coal smoke does not act as an irritant, causing discomfort or inflammation on the body tissue with which it comes in contact, as does ordinary dust. And since there is relatively little coal dust in the air, it is inconceivable that it should have much pathological effect. (2) The researches of Arnold tended to show very slight harmful effects from coal dust in comparison with other forms of dust. In answer to these contentions, Ascher asserts that the action of smoke cannot be represented as an inflammatory one due to mere physical ingredients. Since smoke consists in the greater part of chemical ingredients, the effect upon the human lungs is rather an indirect than a direct one, due to the fact that the normal constituents of the air are replaced by abnormal ones. In order to obtain relevant statistics concerning the effect of smoke upon health, it is necessary to assume that smoke belongs to the same category of harmful agents which have an indirect predisposing effect, such as alcohol, unsanitary dwellings, etc.

Another reason which has been urged against the harmfulness of smoke has been the fact that coal miners show an especially favorable death rate from tuberculosis. According to statistics, very few miners die from tuberculosis. Ascher claims that an explanation of this can be found in the fact that they die of acute lung diseases. The death rate among miners from acute lung diseases is much higher than among other inhabitants of the same age in Prussia. Again, he states, every miner becomes within forty years an invalid and is then no longer considered in the statistics. From this apparently low death rate from tuberculosis amongst coal miners has arisen the belief that coal dust, smoke and soot were not only not harmful but even beneficial to health. Ascher has compiled the following table to show the fallacy of this view:

TABLE I.

Fifty-Fifth Annual Report of the Registrar General of the United Kingdom.

Death Rate per 10,000.

	T.	NT.
Laborers in Agricultural Districts	18.8	18.6
Coal Miners	14.10	32.6
Chimney Sweeps and Soot Merchants	37.1	43.1
Coal Heavers	29.7	65.6

Here it is apparent that, while the death rate from tuberculosis appears low among coal miners, it is not low among other laborers working in coal dust and smoke. Coal carriers, chimney sweeps, and soot handlers show a high mortality both from tuberculosis and non-tuberculous disease. Ascher maintains that the low mortality from tuberculosis among coal miners is due to the choice of picked workmen, selected for hard work, and who earn a higher scale of wages and live under good social conditions. Hence, the better physical and economic conditions of coal miners serves to explain the low death rate from tuberculosis. These same conditions ought to reveal a

lower mortality from non-tuberculous lung diseases, but as a matter of fact the death rate from such diseases among miners is far above the average.

From German statistics, Ascher found a similar state of matters among coal miners.

TABLE II.

Death Rate per 10,000.

	T.	NT.
Workmen in Prussia (15-60 yrs. of age)	28.8	16.5
Coal Miners in the Ruhr District	13.1	39.2

Here, again, Ascher explains the low death rate from tuberculosis among miners as due to the fact that they are very robust and earn high wages. The high death rate from non-tuberculous lung disease is again very striking.

Statistics of the mortality from tuberculous and non-tuberculous lung diseases for the whole population of Prussia are given in the following table:

TABLE III.

Death Rate per 10,000 of Population.

	T.	NT.
1875-1879	31	16
1880-1884	31	20
1885-1889	29	22
1890-1894	25	22
1895-1899	21	26
1900-1904	19	27

This table shows for Prussia a striking decrease in the death rate from tuberculosis and an increase in other acute lung diseases.

He further compared the death rate of infants in agricultural and industrial districts of Prussia:

TABLE IV.

	East Prussia (agricultural)			Silesia (industrial)			Rhine Province (industrial)		
	NT	S&M	D	NT	S&M	D	NT	S&M	D
1876	4.0	3.1	13.7	3.4	10.9	4.4	3.7	2.1	2.8
1880-81	1.6	4.7	34.9	5.0	8.7	5.5	6.4	3.4	3.6
1885-86	3.4	18.2	30.3	7.3	7.8	8.6	12.2	4.1	2.6
1890-91	4.2	9.9	25.0	10.7	4.1	7.9	15.3	2.3	2.1
1895-99	5.9	7.4	13.9	15.2	3.9	3.2	16.7	2.7	2.2
1900-01	6.9	7.1	10.5	19.4	6.4	2.7	21.2	2.8	1.6

S. (Scarlet Fever.)   M. (Measles.)   D. (Diphtheria.)

An analysis of the death rate of infants under one year of age for the period 1876-1901 in certain rural districts and industrial districts of Prussia showed the following:

Death Rate per Hundred Under 1 Year of Age.

	NT.	Scarlet Fever, Measles, Diphtheria, Croup.
In six rural districts of East Prussia	4.3	29.8
In six industrial districts of Rhineland	12.6	5.2

He points out here that the contrast between acute lung diseases and contagious diseases among those who are most subject to them, viz., children under one year of age, is very great. This table proves that the higher death rate from acute lung diseases in the Rhenish districts is not due to worse economical conditions nor a more unfavorable climate, for the six districts of East Prussia have a considerably poorer population than the six industrial districts of Rhineland. The former also have a

longer and harder winter and a climate subject to great
variations of temperature, whilst the six Rhenish districts
have a mild and even temperature. Here, he states, we
see a rapid rise of NT diseases, both in the Silesia and
the Rhine industrial districts, an increase of from 500%
to 600% during a period of 25 years. That such increase
is not merely an expression of increased opportunity for
infection is clearly proven by the varying behavior of the
death rate from the infectious diseases, scarlet fever,
measles and diphtheria, the death rate from the latter
being highest in the agricultural regions of East Prussia
and much lower in the industrial regions.

The death rate of infants in rural and urban districts
is again compared in the following table:

TABLE V.

	NT.		Acute Infectious Diseases	
	Male	Female	Male	Female
Country	6.24	5.19	25.37	23.81
Small Town	12.61	10.52	18.10	17.75
Medium Sized Town	17.33	15.34	11.36	11.48
Large City	26.30	23.34	10.52	10.52

This table shows significantly an increase in acute
lung diseases and a decrease in infectious diseases.

The mortality of infants from acute lung diseases for
a period of years in the whole of Prussia is shown in the
following:

TABLE VII.

Death Rate per 1,000.

	Male	Female
1876-1879	8.3	6.9
1881-1884	11.6	9.6
1885-1889	13.1	10.9
1890-1894	17.3	14.5
1895-1899	20.2	16.2
1900-1909	22.10	17.7

This constant increase in the death rate among infants Ascher believes can be attributed to the increase in smoke. Smoke and soot in small quantities decrease the resistance, especially in weakened individuals, *i. e.,* infants and the tuberculous.

For the purpose of comparing the rates of death for tuberculous and other acute lung diseases, Ascher has taken some statistics from England:

TABLE VIII.

Deaths in England for Every Million of Population.

Years	1850-4	1855-9	1860-4	1865-9	1870-4	1875-9
Tuberculosis	3655.0	3448.0	3367.6	3326.0	3013.4	2903.0
Acute Lung Diseases	2769.0	3155.2	3409.2	3415.4	3607.2	3981.0
T : NT.	1.34	1.09	0.99	0.97	0.84	0.75

Another table for a later period shows:

TABLE IX.

	1881-85	1886-90	1891-95
Tuberculosis	18.30	16.24	14.63
Bronchitis Pneumonia Pleurisy	32.09	33.22	33.63
T : NT.	0.57	0.49	0.43

Both tables show a progressive decrease in the ratio, a lowering of the death rate from tuberculosis, and an increase in acute lung diseases.

Ascher's next step was to undertake a comparison of the death rates in smoky and textile districts. He cites the work of Finkelburg, who showed that the mortality from affections of the bronchial tubes is more than half as great again in towns as in the country and, moreover, that it rises to an unusual height not in textile towns, but in places where coal is burned. Ascher's own investigations corroborated the findings of Finkelburg. He con-

trasts the statistics obtained for Krefeld, a typical textile town, and Essen, a smoky town.

TABLE X.

	KREFELD (Textile)			ESSEN (Smoke)		
	T	NT	T:NT	T	NT	T:NT
1876	5.92	0.61	9.7	4.70	1.18	4.0
1880-81	4.87	1.48	3.2	4.21	3.37	1.2
1885-86	5.37	1.49	3.6	3.66	4.12	0.9
1890-91	3.83	2.81	1.4	2.98	4.48	0.7
1895-96	3.10	2.49	1.2	2.12	3.79	0.6
1900-01	2.37	2.50	0.9	1.91	5.05	0.4

He concludes from this that we always find tuberculosis in textile districts and acute lung diseases in smoky districts.

He has employed the following table, taken from statistics of the Royal Prussian Offices, to show that the mortality from acute lung diseases is 30% higher in smoky than in textile districts:

TABLE XI.

Mortality per 1,000 of Population.

	T	NT	T+NT	T:NT
Textile Districts	1.83	2.23	4.06	0.82
Smoky Districts	1.77	2.93	4.70	0.62

A selection of a group of non-industrial and industrial districts has offered a striking contrast of the frequency of non-tuberculous and tuberculous mortality in the two classes. The statistics are taken for the period 1898-1907.

TABLE XII.

Death Rate per 10,000.

Non-Industrial Area			Industrial Area		
	NT	T		NT	T
Amsberg	28.19	23.59	Dortmond	36.88	14.99
Meschede	26.99	27.35	Bochum	35.89	13.78
Brillon	24.50	29.36	Gelsenkirchen	37.35	15.20

In analyzing this table, Ascher points out that the three industrial districts are wealthier and, for that reason, presuppose a lower death rate from tuberculosis, but they also have a more smoky atmosphere and therefore a higher death rate from acute lung diseases.

For the purpose of establishing the fact that this pernicious influence of smoke is active at all stages of life in increasing the death rate from acute lung diseases, he has compared the statistics from two equally large towns, situated in close proximity, in the industrial district of Westphalia. These towns are built in the same style and differ only in the amount of coal smoke in the air. The town of Hamm, which lies easterly, receives coal smoke only from the west, while Gelsenkirchen, situated centrally, has an atmosphere constantly charged with smoke.

TABLE XIII.

Death Rate per 10,000 during years 1900-1902.

	Hamm Pop. 32,435 30.6 NT	Glesenkirchen Pop. 37,834 57.4 NT
According to age		
0-1 years	228.9	258.9
1-5 "	57.1	131.1
5-10 "	6.5	17.3
10-15 "	1.8	2.6
15-60 "	10.7	34.7
60+ "	140.7	210.2

The influence of smoke here in raising the death rate from acute lung diseases is quite apparent. A similar cause, he believes, serves to explain the increased death rate found in the industrial regions of Westphalia and Upper Silesia, as noted in the following table:

TABLE XIV.

Death Rate per 10,000. Years 1905-1909.

Death rate from acute lung diseases in all German towns with 15,000 of a population or more	24.0
In equally large towns of Rhenish Westphalia (industrial area)	34.0
In the industrial districts of Silesia	36.0

A study of urban and industrial districts in England yielded a similar result. The average death rate from acute lung diseases for the industrial urban districts was found to be 26.5 per 10,000, and for the rural counties only 17.5.

The later studies of Ascher have disclosed a significant fact in regard to the relation of smoke to tuberculosis. He has demonstrated that tuberculous patients, both male and female, die at an earlier age than formerly. For the year 1876, of every 100 persons dying of tuberculosis in Prussia, 36.64 male and 32.64 females were over fifty years of age. Later, in 1901, only 28.20 tuberculous males and 23.54 females survived the age of fifty. Rahts has similarly shown that of every 1,000 persons of all ages dying of tuberculosis, in the city 112, and in the country 206, have passed the age of sixty. These figures would seem to justify the conclusion that with increasing industrial activity and a thickening of the population, there arises a greater deterioration of public health, not necessarily an increase in the mortality but an earlier age of death. Since the mortality from tuberculosis and other lung diseases is dependent inversely upon the resistance of the individual, the earlier age of death in industrial districts is not to be attributed to an earlier opportunity for infection, but to a lowering of the power of resistance. The factor which causes a lowering of the resistance, Ascher believes, lies in the presence of smoke from coal fires.

Again, Ascher maintains that the tuberculous lesion *per se* does not cause the death of the individual, since the tendency of such a lesion is always towards healing, a

fact readily demonstrated by pathological investigation. The fatal results are due to the secondary infection of the lungs with other micro-organisms, such as the streptococcus, pneumococcus, or influenza bacillus. Therefore, he states, "we can easily imagine that a harmful factor which increases the disposition towards acute lung diseases causes a quicker course in tuberculosis." A proof of this was seen in the influenzal epidemic in Germany in which the tuberculous patients died very quickly. From these facts, Ascher concludes that smokes causes a predisposition towards acute lung disease and hastens the course of tuberculosis.

Ascher hoped to confirm his statistical studies by means of pathological examinations of human subjects. He was unable, however, to obtain sufficient material and was obliged to forego this line of investigation. His animal experimentations were more successful. The points he sought to elucidate were:

1. Does smoke cause a disposition to acute lung disease in rabbits, *i. e.*, are rabbits which have breathed smoke for some time seized by acute lung disease, and are animals not so exposed less liable to contract such disease?

2. Does smoke cause a more rapid course in pulmonary tuberculosis, *i. e.*, do rabbits which have been innoculated with tuberculosis die more quickly if they have inhaled smoke than if they have not?

In order to investigate these questions, ten rabbits were innoculated with tubercle bacilli and these, together with ten control normal rabbits were exposed from 90 to 120 days, 10 hours daily, to a smoky atmosphere. The innoculated animals died on the average of 53.9 days, while the tuberculous control animals lived almost double the number of days, or an average of 90.3 days. In addition to tuberculosis of the lungs, other conditions which developed were bronchitis, purulent pneumonia, and peritonitis. Nor was the smoke, indeed, quite devoid of effect on the entire organism. Some of the rabbits exposed to smoke showed eczema, loss of hair, and scaling. The amount of coal dust in the lungs was small, as a rule,

except in unaffected parts where, at times, it was found in abundance. He also found that moisture combined with smoke intensified its effects. Similar, but less distinct results were obtained by causing animals to breathe soot. The same predisposition to acute lung disease and a quicker course of tuberculosis was demonstrated.

From these statistical and experimental studies, as yet the most comprehensive found in the literature dealing with the smoke evil, Ascher has drawn the following generalized conclusions:

1. The mortality of acute lung diseases is certainly increasing, especially among children and old people. The cause of this increase is due to the impurification of the air by smoke because, in the first place, the increase is greatest in industrial centers and not in agricultural districts. Since 1875, the mortality from such diseases among nursing infants has increased as much as 600%.

2. Within industrial districts a difference in mortality can also be noted, the death rate from acute lung diseases, in districts with a strong smoke development, being higher than in other industrial centers, e. g., textile districts.

3. The mortality among coal miners from acute lung diseases is a much higher one (135%) than among the other male population of the same age. Here also differences can be observed in that in districts with a larger native population the mortality from acute lung diseases is a higher one than in districts where the miners have lately moved from agricultural districts.

4. The conclusion already noted, that the impurification of the air by smoke causes a predisposition to acute lung diseases and hastens the course of tuberculosis.

As was to be expected, Ascher's conclusions have elicited more or less criticism in certain quarters. Indeed, Ascher himself admits that not all doubts as to the assumption of smoke *per se* being the one factor in causing an increase in the mortality from acute lung diseases, and in hastening the course of tuberculosis, have been eradicated. It is conceivable that there may be other contrib-

uting causes which future scientific studies of the problem will be able to demonstrate.

Liefmann is an investigator who has reviewed Ascher's work and corroborated much of it. He further points out that the small industries are more culpable than the larger ones where special attention is apt to be paid to smoke consumption. He regards the supposition that smoke breathed is a menace to health as difficult to prove, and concerning the statistics of Ascher writes:

"Even though the statistical results would scarcely be in a position to give infallible proof the harmfulness of smoke, when considered along with other evidence, they have considerable weight. The high mortality from acute lung diseases among miners should cause serious reflection."

Renk is another investigator of note who would seem to regard the effects of smoke upon health as general rather than specific.

Bartel and Neumann obtained results comparable to those of Ascher in a series of animal experimentations. In experimental inhalation of tubercle bacilli by guinea pigs, these authors found that guinea pigs which had inhaled a moderate amount of smoke on account of their being kept in a large city, died from pulmonary tuberculosis in less time than those which showed smoke-free lungs.

The Sixty-sixth Annual Report of the Registrar General of England discloses the fact that there was an increase in the mortality from bronchitis and pneumonia in England during the quinquennium 1891-1895, and a considerable decrease since then. In connection with this fact Chubb has observed that eighty cities, London, Manchester, Liverpool, *et al.*, have reported a decrease in smoke since that time.

Very few observers have attempted to explain the manner in which air polluted by smoke and dust acts injuriously upon the body tissues. Bachman is one of the few who has offered an explanation. He believes that the blood of people living in cities with vitiated air becomes

impoverished, resulting in an anaemia (or better, dys-aemia). This, he states, is apparent in the skin of the city dweller. The effect is not due to a local action upon the skin, but to an admixture of such air in the blood of the lung capillaries. The presence of carbon dioxide, sulphuric acid, etc., in the air inspired acts as a protoplasmic poison interfering with cellular activity and causing an inhibitory action on the ciliated cells of the respiratory tract. When the function of these ciliated cells is interfered with, only coughing and hawking can clear the bronchial tubes so as not to plug up the bronchioles. The organism has, he states, a further protection in the lymphatics and leucocytes, but eventually these auxiliary aids are insufficient to cleanse the air and the whole lymph system becomes flooded with the taking up of poisons. The lymphatic glands constitute the third protection against the dust particles. In this condition of chronic impurity of the blood, the organism suffers and is rendered predisposed to infection with pathogenic germs. The author believes that arteriosclerosis may result from this chronic poisoning. "By breathing impure air we render the body fluids impure, and this leaves the body more prone to disease."

(B) THE EFFECT OF THE INDIVIDUAL CONSTITUENTS OF SMOKE UPON HEALTH.

Smoke is composed of solid carbon particles, or soot, and certain volatile gases such as carbon dioxide, sulphur dioxide, sulphuric acid, and other compounds. We shall consider seriatim the more important of these.

Soot.

In the literature, this term is employed with more or less latitude, at times more broadly as synonymous with coal dust, and at other times as referring simply to carbon particles. Concerning the nature of soot, Cohen defines it as consisting mainly of tar and mineral matter ash, to-

gether with small quantities of sulphur and nitrogen compounds, and frequently possessing an acid character. Various analyses show considerable variation in its composition. Soot is a product of incomplete combustion, and domestic soot, as compared with boiler soot, is said to be richer in carbon and the volatile products such as tar, ammonium chloride, and sulphate, and poor in ash. Russell, of London, first observed that soot contains sulphuric acid, the quantity, as estimated by Cohen, varying from 0.28-1.62%. According to Ascher, soot contains about 31% of mineral particles, principally silicates and iron.

The question of the fate of the inhaled carbon particle has been one that has evoked much discussion. It has been generally believed that it may enter the lung either by inhalation or by absorption from the intestinal tract and the lymphatic system. Since Villaret in 1862 suggested the probability of an intestinal origin of pulmonary anthracosis, many investigations to establish or disprove his claim have been made. His assertion that soot gets into the blood stream through the intestines has not been corroborated. As a result of a series of experiments, Arnold admits the presence of carbon particles in the interior of the intestinal tract, but never in the intestinal wall or in the lymph vessels and mesenteric glands, except in isolated instances, where barely a few pigmented cells could be seen in the intestinal tissue and in the mesenteric glands. Aschoff, Schulze, Cohen and Beitzke, in experimenting with China ink introduced into the abdominal cavity, found that this was absorbed by the lymph ducts of the mesenteric glands and of the diaphragm, the thoracic duct, the vena mammaria interna, and the blood. Thence they found it entered the bone marrow, the spleen and the liver, but not the lungs. The evidence of these authors would appear to prove that anthracosis of the lungs is caused directly by inhalation. Calmette, Guerin, von Behring and others, from experimental data, believe that particles absorbed in the intestinal tract may be carried by the lymphatics to the lungs. Oliver inclines to the latter view as a possibility "but that on this account the

intestinal canal should be regarded as the mode by which the insoluble dust more frequently reaches the lungs, rather than by direct inhalation, I am not prepared to admit. The engagement of the lymphatics in the deeper structure of the bronchi and around the blood vessels suggests the possibility of an intestinal source of infection, but the changes observed in the alveoli of the lungs in the early stages of anthracosis points to the irritation of the epithelial lining by direct contact with dust."

Oliver further points out the danger from continual exposure to dust as a factor in producing structural changes in the lungs, such as the replacement of the normal spongy tissue by fibro-connective tissue. He regards pulmonary fibrosis in the early stages as due solely to the irritation by dust. Von Behring believes that pulmonary tuberculosis in such fibrosed lungs frequently develops from the lighting up of disease long latent in the lymphatic glands as a result of a probable intestinal infection contracted during childhood. Oliver cautions persons who are employed in dusty occupations and to whom, as a result of exposure to dust, the ciliated epithelial cells of the trachea are lost, carefully to rinse their nostrils with warm water before leaving the factory.

The manner in which the carbon particles penetrate into the lung tissue after being inhaled is another mooted question. The earlier observers believed that the individual coal particles, because of their inherent hardness and angularity, bored into the tissue, while a later view is that the dust particles are drawn into the tissue by the migrating dust cells. Knauff believes that the dust penetrates the tissue both free and attached to cells. Ruppert maintains that the greater part of the dust enters the tissues without being attached to cells, since he found no evidence of inflammation around pigmented areas. He does not regard it as probable that coal, in the form of soot particles, has the physical strength for boring into the tissues, although this might be a possibility for other forms of dust.

Ruppert conducted a number of animal experiments in the Polytechnic Institute, Heidelberg, upon dogs and rabbits for the purpose of elucidating the following points:

1. What changes are caused by the inhalation of the dust in the epithelium of the air passages in the deeper tissues of the organ of respiration?

2. How does the dust penetrate into the tissue, in a free state or enclosed in cells?

3. What passage does it use in entering?

4. What forces impel it forward in the process?

From the results of his experiments he writes: "So little injurious was the soot to the respiratory organs of the animal that even weak animals can be exposed to the smoke for weeks without suffering particularly." In order to force a sufficient amount of soot into the respiratory passages, he was obliged to tracheotomize the animals. He believes that when dry coal dust is in the form of soot it is less irritating than other forms of dust, e. g., stone dust. When, however, it is suspended in a fluid, as in the experiments of Slavjansky, it has an important irritating effect. The latter found severe acute pneumonia in many cases, but such changes rarely occur except when large quantities of dust have been inhaled. From Ruppert's experiments the conclusion may be drawn that soot is less harmful in its effects on the respiratory organs than the various forms of mineral dust.

Other writers express a similar opinion, that soot, per se, is not especially harmful, and the fact would seem to be fully well substantiated that non-carbonaceous dust (mineral and other) is more serious in its effects upon health than is carbonaceous. Sir James Crichton Brown states "that of all mineral dust carbonaceous dust seems to be the least injurious to the human organism. * * * Besides being in some degree antiseptic, carbon dust is less irritating and scarifying than many other industrial dusts, and it is really by their irritating and scarifying power that the lethal effects of dusts are to be measured." Dr. Evans of Chicago writes: "Smoke carbon is probably as little harmful as any solid which can be taken into

the human body. It is quite inert chemically. Physically, it irritates but little. The harm that it does is that it transports bacteria and secures entrance for them where alone they would be repulsed."

The question as to whether soot and coal dust possess active antiseptic properties has long been a subject for dispute. Formerly, soot and coal dust were believed to have an inhibitive action on the growth of the tubercle bacillus and tuberculous lesions. An evidence of this belief is found in the fact, cited by Jacobi, that the metal grinders of Sheffield had, until twenty-five years ago, the habit of going into places filled with coal dust after having been in the metal dust all day. The majority of such artisans contracted "Grinder's Asthma," which at present is regarded as tuberculous. This belief in the protective power of soot is now known to be largely erroneous, and Mendelssohn, as early as 1885, stated that he had met many persons dying from tuberculosis whose symptoms never showed themselves until they worked in coal dust and smoke.

Oliver thinks that soot acts in a manner different from coal dust. "Soot," he states, "increases the action of incipient tuberculosis, whereas coal dust has an unfavorable effect on the tubercle bacilli. Soot has only a mild action in preventing infection by tuberculosis, whereas coal dust is active in its immunizing qualities. The acid elements of the soot are not only an irritant, but an aid to tuberculous development. * * * It is a common experience that the course of pulmonary tuberculosis is hastened by living in a smoky atmosphere. Also that smoke predisposes to acute lung diseases. Soot differs from coal dust in being a spongy material capable of absorbing sulphuric acid and hydrochloric acid up to 10%, besides retaining other free acid gases and certain oxidation products of a tar-like nature."

According to Lehman (cited by Oliver), the sulphur-dioxide contained in soot is absorbed by the nasal mucous membrane and the particles of carbon are carried further into the respiratory passages, and are finally deposited in

the lung tissue, having meanwhile in their descent given up to the bronchial mucous membrane and the lining membrane of the lungs some of the acids which they retained.

Cornet, by means of animal experimentation, demonstrated that soot did not contain any qualities which would stop or inhibit the tuberculous process.

A number of pathological conditions in the respiratory organs have been attributed to the deposit of soot and coal dust in the lungs by different observers. True it is, that the burden of opinion, until recent years, has been that anthracosis was a condition productive of no specific phenomena of disease, and that lung lesions were independent of the inhalation of dust, and further, that coal miners were almost always immune to tuberculosis. Of late, these older views have been questioned. One condition that has been ascribed by Seltmann and others to a deposit of coal dust in the lung is that of dyspnoea. As quoted by Schlockow: "Seltmann came to the conclusion that a deposit of coal in the lungs, as soon as it reaches a certain degree, diminishes the gaseous exchange by decreasing the breathing surface, checks the formation of blood, and so causes anaemia and dyspnoea." Croque similarly attributes the dyspnoea of miners to anaemia which he regards as due to the faulty aeration of the blood in the lung capillaries around which the deposits of coal press upon the vessels so as to interfere with the flow of blood. He offers no explanation of the fact that many cases of anthracosis are not accompanied by dyspnoea.

Chronic bronchitis and emphysema are two further associated conditions towards which the inhalation of coal dust and soot is believed to exert a predisposing influence. The frequency of chronic bronchitis among coal miners is a well-known fact. Hirst believes that the inhaled particles of coal dust clog the bronchial secretions. Tobold states that the carbon itself of smoke is deposited in the nose, throat and bronchi in a fine form which acts as an irritant causing morning cough. The ciliated cells are no longer able to cope with the deposit of carbon and a chronic inflammatory condition of the mucous membrane

results. It is commonly observed clinically that emphysema follows in the train of chronic bronchitis. Merkel explains this as due to the fact that during spasms of coughing the glottis becomes compressed and the air is forced through the lower bronchi, causing distention of the alveoli and ultimately of the thorax as a whole.

Schlockow regards the dust in the air of mines as especially well adapted to produce emphysema, since certain parts of the lung tissue, due to the deposit of coal dust, are thrown out of function either temporarily or permanently. This entails increased function in the remainder of the lung tissue and, as a result, an abnormal distension of the pulmonary alveoli. Ultimately, as this phenomenon is repeated, the pulmonary vesicles lose their elasticity and become permanently distended. Racine asserts that coal dust may cause emphysema directly through this excessive inspiratory distension without the initial factor of chronic bronchitis. Every inspiration of dust laden air entering the aveoli tends to obstruct them. Each following inhalation introduces more air which, on account of these partly occluded alveoli, must find other air space. Gradually, the open air cells have an increased function thrust upon them and permanent distension results. As a proof of his view, he cites the case of two healthy young miners in whom dyspnoea developed, due to their using lamps producing an unusual amount of soot. After leaving the mine, the dyspnoea gradually disappeared but within a year in each of the miners emphysema developed without the presence of any previous bronchitis.

Concerning the incidence of chronic bronchitis and emphysema among the miners in his district, Racine has compiled the following tables:

TABLE XV.

Among a total of 870 miners there were the following reports of illness for the years 1880-1882:

	1880	1881	1882
From all causes	221, or 27.8%	242, or 29.8%	273, or 27.1%
Chronic Bronchitis	16, or 7.2%	15, or 6.2%	18, or 6.5%
Emphysema	18, or 8.1%	19, or 7.9%	23, or 8.5%

The average for these years was
For Chronic Bronchitis   6.6%
For Emphysema   8.1%

The deposit of coal dust in the lung tissue has been regarded as the exciting factor in the causation of pleurisy. The occurrence of a dry fibrinous pleurisy is frequent among coal miners. Racine, along with Merkel, believes that this may be due to a rather large deposit of coal dust in the neighborhood of the lung periphery, acting as an irritant.

A more remote injury to lung tissue dependent upon the presence of coal dust in the lungs, as observed by Seltmann and Eulenberg, is the production of small cavities, following a localized pneumonia or a limited gangrenous process within the lung tissue. They found that such areas presented the appearance of an inky fluid and at times contained pus. Racine believes that the limited necrosis is due to the pressure exerted by the deposit of large amounts of coal dust, exciting inflammatory changes which result in the formation of abscesses and cavities.

Regarding the disputed question of the inhibitive action of soot against a tuberculous process in the lungs, Racine's views are somewhat at variance with those of Ascher. He states: "My own observation leads me to ascribe to anthracosis of the lungs a protective influence against tuberculosis." He believes that soot has consid-

erable disinfecting power, and that its presence is deterrent against the growth of bacteria.

Coullard has made an exhaustive study of the effect of smoke upon the health of firemen, and his observations are of interest in their bearing upon the problem of industrial smoke and health. He describes the following symptoms arising from the inhalation of soot:

1. Effect upon the eyes. Redness and congestion of the conjunctiva, accompanied by copious tears and a sensation of prickling, as of a foreign body in the eye. In cases of severe irritation, the ciliary glands, and the lachrymal glands also, may be inflamed; or still more serious ailments (including a hypersecretion).

2. Effect upon the nasal passages. The carbon particles or heavy vapors, inhaled through the nose, cause a rapid inflammation of the nasal mucous membrane. This congestion is accompanied by hypersecretion and is frequently complicated with the frontal sinus. This inflammation is the frequent cause of frontal headaches.

3. Effect upon the pharynx. Very frequently in firemen, enlargement of the tonsils is found, which Dr. Henning of Leipzig does not hesitate to attribute to the irritating effect of smoke. Redness and congestion of the pharynx are very frequent.

4. Effect upon the respiratory organs. Irritating smoke causes inflammation of the larynx which may even develop into oedema, or swelling of the glottis, the irritation being most often betrayed by a dry, spasmodic, and very painful cough. The vapors and particles of smoke penetrate into the trachea and the bronchial passages, and in individuals subject to emphysema, or cough, bring on asthmatic symptoms. In extreme cases, bronchial pneumonia and lobar pneumonia may result, but most often pneumonia, in the case of firemen,

is attributable to the cold caused by the great quantities of water poured upon the fire.

This author further employed animal experimentation in pursuing his study concerning the effect of smoke. From the results of his experiments he concludes that the carbon particles play a large role in the production of serious symptoms. He believes that a certain number of slight disorders, frequently observed in firemen, are due to the action of carbon particles upon the mucous membranes, but he states "although it is true that animals poisoned by filtered smoke (e. g., smoke from which soot has been withdrawn by filtering) return to life more easily than those which have been subjected to common smoke," he yet maintains that the poisonous gases of the smoke are responsible for the grave symptoms produced by the inhalation of smoke among firemen, rather than the soot.

Apart from its more obvious effect upon the respiratory organs, soot has for many years been more or less fancifully believed to create a predisposition towards the production of cancerous growths among workmen who are brought into contact with it. Only recently Sir Thomas Oliver has again called attention to this possible relationship. While the handling of coal itself is not apparently attended by any risk from cancer, there is some evidence for the belief that working with soot does seem to predispose towards it. To quote from Oliver: "In Great Britain we are familiar with chimney sweeps' cancer. Something, therefore, is present in soot in a chemically active form which irritates the skin and leads to cancer. That the scrotal cancer of chimney sweeps is the result of irritation caused by soot is confirmed by the youthful age and occupation of its victims. Years ago, Earl published notes of three cases of cancer occurring on the hands of gardeners, who had been distributing soot among plants. All the men were under the age of thirty. Earl's father described a case of cancer of the scrotum in a boy eight years of age who was a chimney sweep, and Sir James Paget observed the disease in the ears of workmen who had carried sacks of soot on their shoulders. Mortality

figures show that in England and Wales cancer among chimney sweeps is twice as frequent as in occupied males generally. The comparative mortality figures for cancer among chimney sweeps between the ages of twenty-six and sixty-five was, for the three years ending 1903, 133, as compared with 63 for occupied males at the same ages. We must therefore admit that the chimney sweeps' occupation is a cause of cancer." It is scarcely conceivable that the amount of soot in the air of industrial towns is sufficient in amount to be an exciting cause of cancer, as it may possibly be in the case of the chimney sweep.

EFFECTS OF THE GASEOUS CONSTITUENTS OF SMOKE UPON HEALTH.

The gaseous components of smoke, which are believed to exert a baneful influence upon health, include carbon monoxide, carbon dioxide, certain sulphur and arsenic compounds, and nitrous and chloric vapors.

CARBON MONOXIDE.

Carbon monoxide is a product of combustion, which is known physiologically to act as a poison on the human organism if inhaled in sufficiently large amounts. According to Gruber, an atmosphere becomes dangerous when it contains 0.05% of carbon monoxide, while Haldane believes that symptoms may be caused by as small an amount as 0.02%. Kinnicut and Sanford state that air containing 0.3% of the gas causes death, 0.2% very dangerous symptoms, and that mice will quickly show the effects of the gas when the air contains only 0.005%. The smoke from iron furnaces, it is stated, may contain as much as 25%-35% of carbon monoxide gas. When present in lethal proportions the principal symptoms produced are severe headache, vertigo, a vague feeling of illness, marked muscular weakness, and frequently nausea and vomiting. If the amount of gas be greater, drowsiness and loss of consciousness and death may result.

Gautier made an analysis of air taken from the open street and found that only 1 part in 500,000 of carbon monoxide, a proportion presumably inert in regard to health. He believed, however, that the air near factories would contain a sufficient amount of this gas to prove a menace to health. Very few estimations of the amount of carbon monoxide in the air of industrial towns have been made.

Fodor, from the results of animal experimentation, concludes that human beings are much more sensitive to the effects of this gas than are the lower animals. "If present," he states, "in greater quantities than 0.15% it is dangerous to health, especially if breathed continually, and when present in quantities of 0.05%, or even perhaps as low as 0.023%, it produces a bad effect." One of the results of long continued breathing of carbon monoxide is the production of a severe anaemia. So violent, he writes, is the action of carbon monoxide that even when an animal has recovered consciousness, after poisoning by carbon monoxide, the danger is not passed; the animal, and likewise the human being, may pay the penalty with his life, although the inhalation of carbon monoxide has ceased. The affinity of carbon monoxide for the blood, or conversely, of blood for carbon monoxide, is such that carbon monoxide is taken into the organism and into the blood circulation when the atmosphere contains no more than .004% or 1/25,000 part." For the reason that such minute amounts are harmful, Fodor does not believe that any minimal quantity is permissible in the air, and he maintains that to be perfectly healthy an atmosphere should contain no trace of carbon monoxide.

Tobold believes that, while the amount of carbon monoxide in our dwellings is not appreciable ordinarily, small quantities of it may cause headache and indisposition. Sambere regards the determining factor of the effect upon the human organism as the proportion of carbon monoxide to the oxygen breathed, rather than the absolute amount of carbon monoxide.

Coullard states that the effects of carbon monoxide and carbon dioxide inhalation by firemen are not, as a rule, very serious. The symptoms produced in firemen are mainly headache, weakness, nausea, and vomiting, fainting, dyspnoea, and a rapid pulse, coldness of the extremities, profuse perspiration with pallor of the face, diarrhoea, neurasthenia, and the development of tuberculous lesions. Practical trials prove that a robust man, entering a smoky atmosphere which contains 1%-1.5% of carbon monoxide, is affected by asphyxial disorders only very slightly serious if he does not remain in this atmosphere more than ten or fifteen minutes. For carbon monoxide to produce very rapid effects, Coullard estimates the gaseous mixture inhaled must contain at least 15% of it—ten times as much as is contained in ordinary smoke.

CARBON DIOXIDE.

According to Renk, normal air contains about .03% and city air about .03%-.05% of carbon dioxide. The air of factories, during the daytime, has about an average of 10.1 volumes per 10,000 of the gas, while at night, when the gas is burning, it has been estimated that there are about 17.6 volumes per 10,000. In an atmosphere in which oxygen has been reduced to 1.5% or 3%, a proportion of 12%-15% of carbon dioxide produces fatal results.

Schaffer states that in London 100,000 tons of carbon dioxide are poured into the air each day as smoke. Every ton of completely burned coal gives rise to about three tons of carbon dioxide and monoxide. According to Tobold, carbon dioxide in a proportion of 1:10 acts as a poison, causing headache and shortness of breath, while if present in a proportion of 30%, death may result. Evans believes that we can stand a much higher percentage of carbon dioxide than is ever found in the outside air, and that while carbon monoxide is directly toxic, carbon dioxide is only depressant and remotely toxic and is never fatal in "one whiff in any concentration." But, as he wisely adds, "neither does a child get a complete education in five minutes in a grammar school."

Coullard studied the poisonous effects of carbon dioxide in observing the effect of smoke on firemen. He states that a smoky atmosphere is sometimes extremely poisonous, due to the presence of quite large quantities of carbon dioxide rather than to a deficincy of oxygen. The fact that Pettenkofer was able to pass several hours in an atmosphere containing 1% of carbon dioxide without being made ill by it lead Coullard to regard this gas as not especially poisonous. Another observer breathed without difficulty for ten minutes an atmosphere in which there was 4% of carbon dioxide.

The effect of carbon dioxide inhalation may be explained as follows, according to Bert (cited by Coullard): "From the accumulation of carbon dioxide in the blood there results a progressive abatement of the oxidation within the organs, and from this as a consequence, a considerable lowering of the temperature of the body. The central nervous system in the general action upon the organism first manifests that it is affected by the loss of reflex transmission, first to the limbs, then to the eyes, then finally to the respiratory center, from which death results without any agitation or convulsive movement."

While the air of smoky towns does not contain carbon dioxide in a proportion sufficient to produce the foregoing results, nor, indeed, to prove instantly a menace to health, yet it is altogether probable, as has been suggested, that "small amounts of excess carbon dioxide, continued for long periods of time would, within limits, tend to have the effects somewhat similar to the effects of large amounts breathed for a short period of time."

Sulphur.

The sulphur compounds found present in smoke occur mainly in the form of sulphur dioxide and sulphuric acid. The amount of sulphur, in this form in a smoky atmosphere, is at times so great that it cannot be disregarded as a probable exciting cause of ill health. It has been estimated that in London 981,792 pounds of sulphur are

poured into the air each day, or over 500,000 tons in the course of the year. In Glasgow and Manchester, it is stated, twenty tons escape each day in the smoke. According to Rideal, the quantity of sulphur found present in the air of London, from different analyses, is from 0.015-0.77 grams per 100 cubic feet. At Kew, as much as 2% of sulphur was found in an analysis of dust from an exposed surface. According to Nicholson, one-half cwt. of sulphuric acid is deposited over every square mile of Manchester, and in Chelsea very much greater deposits.

There is much unanimity of opinion regarding the deleterious influence of the sulphurous gases upon health. Concerning the action of sulphur dioxide on the human organism, Cushny states that 5 parts in 10,000 acts as an irritant causing sneezing, coughing, and lachrymation, and that, in somewhat greater concentration, it becomes entirely irrespirable; still smaller quantities in the air cause bronchial irritation and catarrh when inhaled for some time. Lehman believes that sulphur dioxide in amounts as small as .001% (0.1% being fatal) causes discomfort, and that 3 parts in 100,000 renders some persons decidedly ill after a few minutes. It is the opinion of Harrington that sulphur dioxide affects the digestive tract rather than the respiratory organs.

According to a theory expressed by Markel, sulphur is possessed of a somewhat ferment-like action in the air in its tendency to automatic renewal. This author states that sulphurous acid coming into contact with iron is immediately oxidized into sulphuric acid which, in turn, reacts upon iron forming ferrous sulphate and iron oxide. The latter drops off as rust and begins a new sulphur cycle. It is also commonly known that sulphur dioxide possesses certain disinfectant properties, being germicidal in the proportion of not less than 92 grams of sulphur per cubic metre. The presence of moisture enhances this disinfecting action and at the same time, it is believed, increases the injurious effect of sulphur dioxide upon the human organism.

It is probable that sulphurous fumes are the most deadly of all the gaseous constituents of smoke. In this connection Evans states: "Sulphur compounds are very objectionable and probably more harmful than carbon compounds. Probably before long our dense smoke ordinances will be changed so as to add to the carbon control other provisions which will control sulphur compounds. Possibly, also, the combustion experiments will likewise be directed more to the solution of the sulphur problem."

Coullard's studies among firemen did not lead him to regard the inhalation of sulphurous acid fumes as productive of any very serious disorders. Opposed to this, is the opinion of Schaefer, who has made a special study of the effects of sulphur gases on health, and who attributes lasting and serious results due to the inhalation of these gases. Sulphur fumes, he believes, play a large role in the etiology of asthma. To quote him: "The importance of sulphur dioxide as an impurity of the air of our cities and its injurious effects upon the organs of respiration is a subject that has not reached the attention, in works on hygiene, that it demands. The writer has been studying the noxious effects of sulphur dioxide as an impurity of the atmosphere for the past ten years, and he has arrived at the conclusion that it is one of the most potent causal factors of asthma."

Ascher has cited experimental work done by Kimball on rabbits which demonstrated the fact that, by causing rabbits to breathe small quantities of sulphuric acid fumes, tuberculous infections were increased. The same author states that other experimental work has shown that sulphur inhalation causes a decrease in the bactericidal action in tuberculous lungs and a lowering of the power of resistance.

ARSENIC.

It has been found that most varieties of coal contain small quantities of arsenic, probably in the form of arsenical pyrites. Cohen and Ruston believe that the

arsenic which is found present in the air and water comes from the smuts of coal smoke. Traces of arsenic have been found in household dust (0.010%—0.004%) and an analysis of rain water in London showed 0.003 parts per million of arsenic.

According to Delepine, "the large amount of arsenic in soot causes a marked arsenical contamination of the air in Manchester and may account for the bad effects of air on vegetation." In regard to the effect upon health, he writes: "I have a suspicion that soot from towns where arsenical coal is used is far more irritating to the lungs than pure coal dust. The reason why I say so is that I have noticed there is generally more fibrous tissue produced in the lung in town anthracosis than when the coal is inhaled as dust, for instance in the case of coal miners. Lungs of coal miners may be as black as soot without very distinct evidence of inflammatory reaction whilst, on the contrary, in towns, where the amount of carbon collected in the lungs is smaller, there are frequently capsules of fibrous tissue in the lungs around small masses of carbon which have accumulated, indicating some irritating action on the part of soot. All town dust, as well as town air, is never free from arsenic."

In connection with the influence of arsenic inhalation upon health, Cushny's statement concerning the miners of Reichenstein, who are constantly exposed to arsenic owing to its being contained in large quantities in the ore, is of interest. Concerning these, he writes: "'These people are described by Geyer as shortlived, very subject in childhood to severe rickets and in adult life to dropsies and respiratory diseases; they offer little resistance to microbial infection and frequently present the skin and nervous symptoms of arsenic poisoning."

Nitrogen and Chlorine Gases.

These gases occur mainly in the smoke of industrial centers, especially in the fumes from factories using nitrate of mercury and from chemical works where sul-

phuric acid is manufactured. They probably play a minor role in the effect of smoke upon health. Coullard has called attention to the manner in which they appear to act injuriously. The nitrous vapors act, he states, (1) by powerfully irritating the bronchi and the small pulmonary vessels to the point of producing centers of apoplexy, and (2) by producing a special impairing of the blood." The chlorine fumes, he believes, while slightly irritating, do not cause serious disorders except through prolonged inhalation, in which case it is not uncommon for a tuberculous process to become lighted up.

As a general resume of the effects of the various constituents of smoke upon health, the following note of Mehrsten's is clarifying. This author writes: "It is not even the dust only that is injurious, but it is the invisible products of combustion escaping from the chimney in the form of gases, of which we need to take into consideration only carbonic acid, nitrogen, carbonic oxide, and sulphurous acid. The first two, which are heavy gases, can probably be regarded as injurious only when they are driven directly into dwellings and this cannot happen unless the chimneys are not high enough. The carbonic oxide, which is extremely poisonous, is usually present in such slight quantities that it becomes greatly diffused as soon as it escapes from the chimney. On account of its lightness it also arises rapidly and is lost in the higher strata of air; but, on the other hand, the gaseous sulphuric acid (sulphur dioxide) generated from the sulphur contained in the coal, which is considerably heavier than the air, is such an injurious gas that first of all our efforts must be directed toward preventing it from doing harm, all the more as it is not only the human organism that is injured but also, in a positively destructive manner, the vegetation, soil, and buildings. These facts show that any smokeless furnace with a direct combustion has little value for the public as far as the purification of the air is concerned unless the dust and the sulphurous acid are retained at the same time."

INDIRECT EFFECTS OF A SMOKY ATMOSPHERE UPON THE HEALTH OF THE COMMUNITY.

FOGS.

It is a fact long well known that a smoky atmosphere predisposes towards fogs. When an atmosphere laden with suspended particles becomes charged with moisture a fog is precipitated. According to Nicholson, over 25% of the fogs are caused by smoke.

Not infrequently, following a fog period, there is a sharp rise in the death rate of a community, the rise being due mainly to the great increase in deaths from diseases of the respiratory organs. Scientific observers of vital statistics have here once again placed varying interpretations upon this increase, a few authorities regarding the increased mortality as dependent upon the alterations in the temperature and other factors, while others maintain that the fog, *per se,* is the exciting cause of the increase. Among the former class of conservative writers is W. J. Russell of London, who, in commenting upon the effects of London fogs, writes: "By far the greater number of fogs occur when there is a great fall in temperature, and clearly this is followed closely after a few days by a great increase in the death rate; but how much of this is to be attributed to the fog and how much to the fall in temperature may be difficult to determine, but we have evidence that when fogs occur without fall of temperature they do not appear to be followed by any remarkable increase of the death rate, for on December 15, 1889, there was a dense fog and the temperature was even above the average; under the conditions, the death rate remained far above the average. On December 13 and 14 of the same year there was a dense fog, an average temperature, and only an average death rate; and the same thing happened on February 4, 1890, when, notwithstanding a dense fog, the death rate remained low, and last winter on November 13 and 14 there was a dense fog, a high temperature, and an

average death rate. With these four exceptions, depression of temperature goes with fog. There is no case of depression of temperature not followed by increase of death rate. That many people suffer, both physically and mentally, from the effects of fog there can be no doubt, but so far as I can interpret these returns of the Registrar General, they do not confirm the popular impression that fog is a deadly scourge; at the same time, it is beyond doubt that an atmosphere charged with soot dust and empyreumatic products is an unwholesome atmosphere to breathe; but I think that the principal cause of the great increase of deaths when fogs occur is attributable rather to the sudden fall of temperature than to the fog itself. As to bacteria—the experiments of Dr. Percy Frankland show that fogs do not tend to concentrate or nurture them, for he found that there were remarkably few bacteria in London air during a time of fog."

In the opinion of Rollo Russell, while cold is doubtless a contributing factor in raising the mortality during a fog period, the most potent cause lies in the smoke constituents of the foggy atmosphere. He writes: "Great cold combined with fog is not productive of much illness in the country. In smoky towns, the case is far different. Thus, in London, the death rate was raised in a single fortnight, from January 24 to February 7, 1880, from 27.1 to 48.1 per thousand. The fatality and prevalence of respiratory diseases were enormously increased. The excess of deaths over the average in the three weeks ending February 14 was 2,994, and in the week ending February 7 the deaths from whooping cough were unprecedently numerous, 248, and those from bronchitis numbered 1,223. At least 30,000 persons must have been ill from the combined effects of smoky fog and cold. * * * The large excess of carbon dioxide, sulphurous acid, and of microorganisms and effete organic products was partly concerned in these ill effects, but the factor of greatest importance was the finely divided and thickly distributed carbon, or carbonaceous matter, which irritated the breathing passages and lungs. The results corresponded rather

closely with the gradual ill effects of the dusty trades.
*　*　* After a fortnight of dense fogs, the deaths in
London for one week ending January 2, 1892, exceeded
by 1,484 the average number, being at the rate of 42 per
thousand. Increases took place in the following diseases:
Measles, 114%; whooping cough, 173%; phthisis, 42%;
old age, 36%; apoplexy, 58%; diseases of the circulatory
system, 106%; bronchitis, 170%; pneumonia, 111%; other
respiratory diseases, 135%; accidents, 103%. These re-
sults are in the main attributable to the concentration of
the ordinary London air with moisture and intense cold
to help their deadly work. The majority of the fatal
cases were weakened constitutions, though many were
among the robust. The experience of large towns is that
the power of recovery after illness is less within their
confines than in the country. In fog, the evil influences
of town air are many times multiplied." The same writer,
in another place, contrasts the influence on health of a
country and a London fog by quoting statistics of the
death rates of Croyden and London during the great fogs
of 1880. In Croyden, the number of deaths rose from
35-36 in three weeks, while in London the number rose
2,994 above the average during that time.

Ascher attributes the baneful influence of fog to the
fact that the fog concentrates great quantities of smoke
which is inhaled into the lungs in much larger quantities
from the damp air of foggy weather than from dry air.
This, he claims, has been proven experimentally. More-
over, he studied the mortality tables of Manchester in
relation to fog, and drew the following conclusions: "We
see that the mortality from respiratory diseases and
phthisis increases during a period of fog, while the inci-
dence of contagious diseases is not affected by it, a fact
that has been known in England a long time." He was
of the opinion, however, that it would not be justifiable
to draw an unqualified conclusion regarding the influence
of fog since other attendant conditions might also increase
the mortality from lung diseases, e. g., the sudden fall in
temperature, which usually precedes a fog.

Des Voeux studied the effects of two fog periods in Glasgow upon the subsequent death rate. In the autumn of 1909 there occurred two periods of smoke fog in that city, each of several days' duration but separated by an interval of a few weeks. The death rate rose suddenly during the first period from 18 to 25 per thousand, and during the second week to 33 per thousand, while the death rate in the rural environments of the city was increased only very slightly. It was estimated that 1,063 deaths could be attributed to the foggy weather.

Niven has made a similar study concerning the influence of fog periods upon the death rate in Manchester. He found that when fog periods were charted out and the number of deaths from phthisis and other forms of respiratory diseases tabulated, an unmistakable rise in death rate could be demonstrated occurring within a few days from the onset of the fog. He believes that an increase of micro-organisms occurs during fogs and that thereby a diffusion of bronchitis and other diseases finding entrance to the lungs is facilitated by fogs. The following tables showing the bearing of fogs upon the death rate are taken from his report.

Table I. Showing deaths from phthisis in each six weeks preceding, and in each of six weeks containing or following a fog, for the twenty years 1891-1910, added, the fogs not being of longer duration than six days.

Weeks preceding fogs:

6th	5th	4th	3d	2d	1st
2,192	2,040	2,049	2,135	2,161	2,224

Weeks of fog and following:

1st	2d	3d	4th	5th	6th
2,377	2,468	2,360	2,339	2,334	2,399

"It thus appears that there is an increase in deaths, greatest in the first three weeks but continuing into subsequent weeks. The greatest number of deaths is in the week after a fog."

Table II. Showing deaths from Pneumonia during weeks similarly disposed to fogs, in the same manner for the years 1897-1910, added.

Weeks preceding fogs:

6th	5th	4th	3d	2d	1st
1,351	1,389	1,345	1,442	1,442	1,494

Weeks of fog and following:

1st	2d	3d	4th	5th	6th
1,572	1,638	1,657	1,710	1,631	1,589

"There is here a clearly marked influence on mortality ascribed to pneumonia, greatest in the fourth week following the fog and next greatest in the third week. The effect on pneumonia is clearer than that on phthisis and ites maximum intensity is differently disposed, as if time were required for the development of the pneumococcus and the course of the disease."

Table III. Showing deaths from bronchitis during weeks similarly disposed for the years 1897-1910.

Weeks preceding fogs:

6th	5th	4th	3d	2d	1st
1,317	1,301	1,330	1,526	1,479	1,627

Weeks of fog and following:

1st	2d	3d	4th	5th	6th
1,808	1,864	1,848	1,699	1,729	1,749

"Here the maximum effect is manifested in the first three weeks following, the greatest effects being produced in the second week as in phthisis. The increment observed in the different forms of respiratory diseases before the occurrence of fog is due to the fact that the different fogs interfere from the proximity to each other. Thus,

while the effect of the individual fog is diminished, the total effect in producing an increase in mortality becomes more conspicuous. The increase in mortality from bronchitis, like the increase from phthisis, follows more closely on fog than does that from pneumonia. The processes are probably different. In the case of phthisis and bronchitis, fogs cause congestion; in the case of pneumonia, they probably light up pneumonia. When the fogs are of longer duration than six days, the numbers are comparatively small."

Table IV. Respiratory diseases, other than Phthisis, for the years 1891-1905.

Weeks preceding fogs:

6th	5th	4th	3d	2d	1st
304	312	289	355	363	389

Weeks of fog and following:

1st	2d	3d	4th	5th	6th
394	484	417	398	375	332

"No effect is observable under phthisis. The effect of fogs in producing mortality from respiratory diseases is unmistakable."

DIMINUTION OF SUNLIGHT.

That a smoky town means diminished sunlight in the community is a fact universally conceded, even by such as may be skeptical concerning any direct influence of smoke on health. Indeed, some authorities are inclined to attribute the evil effects of smoke to this decrease in sunlight rather than to its irritating action on the organs of respiration. In this connection, Kister writes: "The development of smoke and soot has without doubt a bad effect upon the daylight and sunshine of a place, and, be-

cause of the hygienic significance of sunshine, is inimical to our physical, or at least our psychical, welfare. But it is not easy to prove such a direct injurious effect of smoke upon our respiratory organs."

The precise manner in which a diminution of sunlight acts injuriously on health is a subject more or less under dispute. It is well known that sunlight is germicidal. Tubercle bacilli quickly succumb to the action of direct sunlight, a few hours' exposure sufficing to destroy their vitality, although they may live indefinitely in darkened surroundings. Quite apart from this bactericidal action there are apparently other factors, in decreased sunlight, which militate against health. Liefman has grouped these harmful influences under three headings. "If," he states, "we group all these experiences in the significance of light for our life and health, and concentrate them upon the problem which here interests us, we shall be led, in my opinion, to the conclusion that a darkening of the atmosphere of our great cities is injurious to health in three ways: (1) An exciting impulse which influences our disposition is weakened and the energy of metabolism, especially as it concerns respiration, is diminished. (2) The illumination and warming of the earth, the water, and the air within the precincts of our great cities is diminished and in this way a series of hygienically important processes is influenced or depressed. (3) The chemical and bactericidal effect of the sun's rays is decreased and thus bacteria, especially the pathogenic ones, are permitted to thrive.

Sir William Ramsay regards smoke as harmful by virtue of its power directly to absorb light, and by its effect in the formation of clouds and fogs which, he states, are peculiarly fitted to absorb the blue, the violet, and ultra violet rays, these being the rays that are especially germicidal. In this manner a diminution of sunshine causes an increase of bacteria, both pathogenic and non-pathogenic, in the atmosphere. The same writer believes that sunlight has a direct influence on the human skin as well as upon mental states.

RELATIVE MORTALITY FROM RESPIRATORY DISEASES AND RECORD OF SUNSHINE

In order to ascertain the possible bearing of diminished sunshine on the mortality returns from respiratory diseases, Niven has compiled the following statistics for the industrial cities of Manchester, Birmingham, Sheffield and London:

Year	PHTHISIS				BRONCHITIS				PNEUMONIA				SUNSHINE (Hours)			
	Manchester	Birmingham	Sheffield	London	Manchester	Birmingham	Sheffield	London	Manchester	Birmingham	Sheffield	London	Manchester	Birmingham	Sheffield	London
1901	2.09	1.73	1.41	1.71	2.22	2.07	1.51	1.62	1.96	1.73	1.45	1.35	1192	1144		1567
1902	2.08	1.65	1.18	1.65	2.44	1.91	1.52	1.71	1.98	1.62	1.45	1.47	928	1048		1228
1903	1.85	1.65	1.36	1.62	1.87	1.73	1.71	1.15	1.87	1.48	1.58	1.28	1119	972	1216	1445
1904	1.98	1.45	1.27	1.70	1.97	2.06	1.51	1.40	2.18	1.72	1.39	1.45	1031	1239	1325	1459
1905	1.56	1.54	1.15	1.50	1.85	1.68	1.56	1.33	1.62	1.55	1.44	1.53	1005	1149	1432	1420
1906	1.71	1.45	1.05	1.53	1.74	1.68	1.46	1.18	1.59	1.47	1.32	1.45	1069	1143	1438	1735
1907	1.70	1.29	1.20	1.51	2.06	1.76	1.76	1.32	2.02	1.66	1.70	1.66	894	952	1428	1417
1908	1.65	1.29	1.28	1.44	1.96	1.73	1.65	1.15	1.75	1.35	1.59	1.46	992	981	1281	1634
1909	1.70	1.39	1.17	1.44	2.00	1.77	1.32	1.35	1.72	1.46	1.54	1.68	999	1129	1332	1641
1910	1.49	1.44	1.01	1.28	1.59	1.51	1.26	1.12	1.40	1.33	1.52	1.49	982	1011		1380

It is difficult to draw any exact conclusions from this table, the evidence presented being, on the whole, somewhat equivocal. A more or less general decrease in respiratory diseases (with the exception of a slight rise in pneumonia in London and Sheffield) may be noted but it cannot be demonstrated that this general decrease is concurrent with an increase in the number of hours of sunshine in the four cities. London and Sheffield show a slight increase in the number of hours of sunshine; Birmingham and Manchester present a continuously decreasing number of sunlight hours.

Some statistics of Kister for the city of Hamburg, one of the smokiest of German towns, are comparable with those of the English towns. The following table is taken from a report of this writer on the Investigation on Smoke and Soot in Hamburg:

MORTALITY FROM NON-TUBERCULOUS DISEASE OF THE RESPIRATORY ORGANS.

For the City of Hamburg.

(Diphtheria and Whooping Cough are not included.)

Year	Under 1 yr.	1-15 yrs.	15-30 yrs.	30-60 yrs.	60-70 yrs.	Over 70	Total	% of Dead	.01% of Living
1894	412	305	17	143	258	173	1308	12.08	21.636
1895	559	400	22	153	289	280	1703	14.50	27.513
1896	509	377	14	152	261	324	1537	14.03	24.204
1897	417	279	20	149	260	246	1371	12.37	20.996
1898	527	309	18	139	245	255	1578	13.51	23.589
1899	405	363	27	158	339	348	1630	13.74	23.807
1900	527	414	20	218	417	1318	2914	16.50	28.935
1901	548	405	19	156	328	324	1780	14.49	24.845
1902	444	293	21	169	369	342	1748	14.55	23.854
1903	390	333	33	177	364	322	1619	12.99	21.674
1904	441	310	22	155	373	313	1614	13.37	21.081
1905	422	315	51	325	265	384	1762	14.09	22.262
1906	535	358	44	296	223	322	1778	14.24	21.768
1907	466	262	62	419	280	429	1918	15.37	22.709

The comments of the author upon this table are, in part: "If we collect the figures for Hamburg, the following (the table) shows a decrease or perhaps an increase

in recent years from other diseases (non-tuberculous) of the respiratory organs. * * * Even though this fact cannot be referred, without further investigation, to the development of smoke, it is one of the phenomena that must be taken into account in the question of the hygienic effect of smoke."

OTHER REMOTE EFFECTS OF SMOKE UPON HEALTH.

The psychological aspect of the smoke nuisance has been dealt with at length in another Bulletin of this series. The present day recognition of the importance of the mental influence of mind upon bodily health is a hopeful sign of the times. It is doubtful whether the maximum of mental acumen and bodily efficiency may for long be preserved in a smoke laden atmosphere. True it is that, at times, certain minds can rise above their environments, but whether the sum total of the mental efficiency of the community can be equal to that of a community living within cleanliness, aerial and environmental, seems scarcely conceivable. Not infrequently one hears the complaint of the casual visitor to a smoky city with respect to a feeling of mental depression provoked by the smoky atmosphere. Certain physicians have pronounced themselves upon this aspect of the problem. Dr. Evans of Chicago writes: "It (smoke) serves to lower the general tone of a community. A spotless town is more apt to be moral than a dirty town. It is useless to try to get a spotless town and leave the smoke. If the air is dirty it is very hard to get the streets, the yards, the clothes, the people clean." C. A. L. Reed speaks in a similar strain: "Physical dirt is closely allied to moral dirt and both lead to degeneracy. It is too much to expect the best results in the public schools that exist beneath the sombre shade of smoke. It is difficult to imbue the young with a sense of the beautiful when the beauty itself is bedaubed with soot." Jacobi believes "that a clean community has the better chance to avoid degeneracy," and

Des Voeux asserts that "dirt and darkness are the twin children of smoke, and to them are closely related poverty, drunkenness and crime."

A further quite obvious factor which renders a smoky town unhealthy is the necessary curtailment of free house and factory ventilation. To open a window carries with it the certain penalty of soiling a curtain, a rug, or a counterpane. The zealous housewife accordingly is prone to guard the cleanliness of her house at the expense of fresh air. Out of door sleeping porches are, for a similar reason, conspicuous by their absence in smoky towns, in contrast with their increasing use in more cleanly modern cities. The fine shower of soot detracts from the comfort of sleeping in the open air and speedly soils the bed linen. Such a more or less universal avoidance of fresh air militates strongly against the health of the community and predisposes its inhabitants to tuberculous and other diseases.

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Pulmonary Arthracosis—A Community Disease

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Definite observations upon the presence and nature of pigment within the lung substance and its associated lymphatic structures are of relatively recent date. Nevertheless, as early as 1717, Ramazzini discussed the presence of carbonaceous material within the lung and indicated an association with definite pulmonary diseases. His observations were made upon various laborers who, through the inhalation of angular stone particles, became predisposed to asthma and tuberculosis. His observations, however, did not suggest that any of the foreign material contained within the lung consisted of a carbon deposit.

Not until Pearson in 1813 studied the problem and applied the term anthracosis or coal miner's lung, followed by a report by Laennec in 1819, was a more acute attention attracted to the subject. Pearson indicated that individual coal particles when inhaled became deposited in the lung tissue and upon the accumulation of larger quantities of this pigment, the lung gave macroscopic evidence of its presence.

This contention was further supported by Gregory, who in 1831, described the pigment in the lungs of a coal miner with definite tissue changes within the organ. Other English authors (Thompson, Simpson and Stratton) made similar observations and indicated the importance of anthracotic deposits as a type of occupational disease.

Although Pearson's views were accepted in England, they were strongly combatted in Germany, particularly by Koschlakoff, as well as by Virchow and Henele, who regarded the coloring matter in the lung substance and in the lymph nodes of haematogenous origin. Virchow did not believe that the lung substance could be penetrated by inert foreign particles. As late as 1855, Barthelmess discussed "pulmonary melanosis" as a progressive pigmentation of the lung resulting from repeated haemorrhages and inflammation. Subsequently, however, Pearson's observations were confirmed in Traube's clinic (1860) where some carbon pigment, presumably having its origin from charcoal, was demonstrated in the lung substance. Since then the deposition of carbon from smoke has been amply confirmed by studies upon human lungs as well as by animal experimentation. The first confirmatory animal experiments were carried out by Knauff (1867) and repeated by Konradi (1869).

In the earlier discussion upon the inhalation of dust, including the carbon particles of smoke, it was indicated that as every one inhaled more or less of it during his lifetime, little pathological change, other than the storage of pigment, occurred in the lung tissue. It was, however, recognized that the inhalation of different foreign substances had a varying effect upon the respiratory organs. It was deemed that carbon pigment had the least harmful effect and, hence, the deposits which were found in the adult lungs, could be disregarded as having any association with respiratory diseases or clinical symptoms during life.

With the admission that the black pigmentation of the lung was the result of the inhalation of carbon particles contained in the air, a considerable controversy began concerning the manner in which the foreign material made its entrance into the tissues. It was not uncommonly observed that the sputum of individuals working in smoky atmospheres would, for considerable periods of time, contain black pigment particles. Some of this foreign material was free, while some was contained with-

in cells. Knauff believed that these cells were desquamated epithelial structures of the bronchi, which had lost their cilia. It was thought that with the active desquamation of the epithelial lining that a more ready access for the pigment to the deeper structures was possible. Sikorsky and Klein both believed that foreign particles were able to pass between the uninjured epithelial cells and directly enter the lymphatics.

On the other hand, Arnold and Schottelius opposed the view of the direct migration of the pigment into the tissues and claimed that the transport was accomplished only through the agency of cellular activity. This phagocytosis they believed could be accomplished by the bronchial epithelium, lymphoid wandering cells and by the alveolar epithelium. Traube thought that the acicular nature of the carbon particles would account for their tendency to pierce the delicate alveolar walls and then to migrate to other parts by the lymphatic channels. Rindfleisch accepted this latter view, laid stress upon the gritty hardness of the particles and believed that through the impact of the air current the particles may be driven through the superficial tissues. He furthermore pointed out that when these foreign particles had entered the lymph spaces they not uncommonly became incorporated within cells having phagocytic properties.

The theory of the phagocytic transport of the foreign particles continued to gain ground but there was no agreement concerning the nature of the active cell. Slavjansky and Ins believed that the leucocytes were most active, while Ruppert, Schottelius, and others believed that the alveolar epithelium picked up the carbon from the air sacs. Arnold was divided in his views, considering that both types of cells were capable of carrying out this function, while, furthermore, he believed that under certain conditions migration of pigment might occur in the absence of phagocytic cells. Even to the present time, observers are not in unison concerning the taking up and storage of the pigment which reaches the lung. The exact nature of the phagocytic cells, and these seem to be the

active participants in the accumulation of carbon pigment in the pulmonary structures, is still in debate. In a recent study, however, it appears to us that Haythorn has conclusively shown that although pigment may appear in a variety of cells, the important cell acting as a carrier from the air sac to the interstitial tissue and the lymphatics of the lung, is an endothelial cell.

Although, in the early days of cellular pathology (1858) the finding of extensive pulmonary anthracosis was unusual, the situation has changed much in the present day. Then, as now, the most intense examples of pigmentation of the lung were found among the coal miners, and it was particularly to these that Pearson, just a century ago referred, when he first applied the name anthracosis to the pulmonary condition. Apparently, early in the last century, in the course of ordinary life the accumulation of pigmented dust bodies within the lung was hardly sufficient to attract the attention. At that time, the use of coal was less general among the housekeepers and the combustion of wood was relatively complete, with but slight pollution of the air. Then, too, coal was not in as general use in industries nor had the use of the steam engine found a definite place in manufacture.

To-day the use of coal forms the main source of energy for the remarkable industries, which began in the middle of the nineteenth century. We need not indicate by figures or statistics the extent to which our progress is determined by the use of coal. Nor is it within our province to indicate the enormous losses entailed in the incomplete combustion of coal. The main fact stands before us to-day that in every city where householders use coal or in which manufactures of any capacity are located, the air shows a greater or less pollution by carbon particles. To-day it is almost possible to gauge the extent of the manufactures within a city by estimating the quantity of carbon in the atmosphere. In other words, what, not so many years ago was a rather unusual aerial condition, to-day forms a constant finding and has added a nuisance which affects the well-being of the community. No longer may we re-

gard the presence of carbon in the air of large cities as a harmless factor. And furthermore, the gradual accumulation of this foreign material within the respiratory tract has a definite effect upon the tissues in reducing their functional activity and in possibly leading to secondary disturbances affecting our general bodily health.

The following observations have been made upon a series of autopsies, in which the deposit of carbon pigment within the lungs was particularly noted. These observations were made upon civilians not engaged in coal mining. The majority of them had been residents of the Pittsburgh district for the greater part of their lives. We were unable to account for the great variation, which occurred in the intensity of the pigmentation among the different individuals, particularly when their respective occupations appear to have had no relation to the amount of the pigment deposit in the lungs. Thus one of the most markedly pigmented lungs was obtained from a peddler, in whose history we could find no particular association with a sooty atmosphere or industry. It is possible that the tissues of different individuals store the foreign particles from the air with different degrees of activity.

Admitting that but few individuals to-day can escape the accumulation of carbon particles in the respiratory system, it may be suggested that the condition should be looked upon as a normal process. This attitude has been the dominant one in the discussion of pulmonary anthracosis. As, however, we must to-day freely admit that individuals living under different circumstances and in different communities suffer unequally from the quantity of inhaled dust, it is impossible for us to designate all of these as normal conditions. That a small amount of anthracosis of the lungs is not incompatible with good health is obvious to all who have observed the condition in many autopsies. That, however, certain communities are subject to greater pollution of the air by smoke than others, and that the individuals in these communities suffer in an equally greater degree from the inhalation of soot and smoke is also obvious to those who have had an oppor-

tunity of comparing the lungs from different localities. The pathologist has no difficulty in recognizing lung specimens from large manufacturing cities.

Thus we are able to observe variations from the almost non-pigmented lung tissue obtained from those living far distant from cities, to the more intensely pigmented lungs, the coal miner's lung illustrating the extreme degree of carbon deposit. There is, however, some difference between the deeply pigmented coal miner's lung and that obtained from the city dweller. The carbon dust as inhaled in the coal mines is considerably coarser than the fine particles of soot found in the city air. Moreover, the dust in coal mines is made up of fine angular and rough particles, while soot is a mixture of a very fine amorphous carbon and ash.

ANATOMICAL CONSIDERATIONS.

The deposition of carbon pigment in the lungs from the dust-laden air is dependent upon the respiratory function and the activity of the lymphatics. The inhaled air with its carbon particles is carried to varying depths into the lung tissue. The major amount of the foreign material adheres to the moist walls of the respiratory passages and never reaches the lung tissue proper. It is possible, and microscopical analysis seems to confirm this, that the foreign material that adheres to the mucous membranes of the nose, pharynx, trachea, and larger bronchi is but rarely carried into the tissues of these tracts, but lying in the secreted mucous, is carried upwards and is eventually expelled. The relatively lesser quantity of dust and carbon which reaches the lung alveoli also becomes adherent to the moist surfaces of the alveolar sacs and then by the activity of certain cells which have been studied and described by Haythorn, these particles are eventually carried into the lymphatics of the alveolar wall where they are disposed of by the lymphatic system of the part. The subsequent distribution is to a great extent determined by the site of absorbtion within the lung. Thus

the carbon particles which have found their way into the air sacs near the surface of the lung, gradually accumulate within the lymphatics of the visceral pleura, while the carbon which is collected from the more centrally placed alveoli, accumulates about the lymphatic channels which drain that particular area. The tendency of this absorbed carbon is to pass from the finer lymphatic channels of the alveolar walls to the larger passages, eventually reaching a lymph node where the onward progress of the particles is impeded by the filtering action of this structure. In the main, the lymphatic drainage of the entire lung converges at the hilus and passes into the peri-bronchial glands located in this part.

The lymphatics of the visceral pleura form an intricate network of channels which surround each lobule. The lymphatics upon the pleural surface of these lobules can, at times, be recognized by the naked eye. Many anastomoses occur and the larger channels drain towards the hilus. Communications between the surface lymphatics and those within the organ have also been demonstrated.

A somewhat similar system of lymphatic channels have been demonstrated about those lobules which lie within the lung. Not only is there a system of lymphatic channels about the lobules, but small passages extend into the individual alveolar walls. Sikorsky, as well as Wittich, claimed to have demonstrated small patent communications between the lymphatic channels in the alveolar walls and the air sacs. By this means, it was suggested, that foreign materials within the air sacs could find a ready passage into the interstitial lymphatic system. In 1878 Rindfleisch suggested similar passages for the entrance of coal pigment into the lung tissues. He believed that the fine dust particles could pass directly from the air sac into the interstitial lymphatic channels without the intervention of phagocytic cells. He did appreciate the role of phagocytosis in the subsequent transportation and storage of the foreign material. It would appear, however, with the most recent studies that the migration of

the dust particles from the air sacs occurs only through the agency of certain wandering cells.

To thoroughly appreciate the progressive pigmentation of the lung substance by the inhalation of carbon particles, the general mechanism of respiration as well as the efficient lymphatic drainage of all the air sacs must be understood. The important conclusions of Beitzke and Most, that the lymphatics of the lung and visceral pleura have no direct communication with those of the head, neck, or abdomen, and the fact that carbon particles are rarely found in the circulating blood, indicate that pulmonary anthracosis is developed through the activity of the respiratory functions alone. It is, therefore, quite out of place, here to discuss the claims of Calmette, and his associates, for the origin of pulmonary anthracosis in the alimentary tract. A more extensive review and study of the relation of intestinal absorption to anthracosis is given by Montgomery. This author from his own experiments concluded that the respiratory route alone was the important one leading to pulmonary anthracosis.

DISTRIBUTION OF PIGMENT BENEATH THE VISCERAL PLEURA.

At first sight, when the lung is examined externally, the distribution of the deposit of carbon pigment seems to be irregular and without any association with the anatomical structure of the lung. The pigment is deposited in small granular masses, which, in their beginning, occupy areas less than of pin-head size. Sometimes it would appear that the deposit is in the nature of lines which, however, on slight magnification are found to be the coalesence of numerous small granular points.

As the deposit becomes more extensive, the pigment is found to follow a definite arrangement and the anatomical structures which, in the non-pigmented lung are not visible, are mapped out by the deposit. Thus the subpleural pigmentation is found to pick out the septa dividing the lobules of the lung. This geographical marking is

more particularly evident in the early stages of the pig-
mentation prior to the diffuse deposition of the pigment
with the consequent obliteration of the early linear mark-
ings. Whereas in the early stages of the deposit, the septa
of the lobules show fine linear deposits of pigment, the in-
creasing accumulation of the carbon leads to an irregular
thickness of these lines and the conversion of them into
small chains of nodules or to the development of flat or
shot-like masses in the sub-pleural tissues. Gradually the
deposit extends from the septa into the tissues of the
lobules until blotches of pigment become prominent. All
gradations, from the finest hair-like lines in the septa,
to diffuse pigmented areas in which the normal color of
lung substances can not be recognized, are not uncom-
monly seen in the same lung.

The macroscopic appearance of the sub-pleural tissues
is a very good gauge as to the actual amount of carbon
pigment contained in the lung. That is, with the deposit
of such an obvious pigment no difficulty is experienced in
distinguishing its presence or in gauging the amount pres-
ent in each portion of the tissue examined. It is well,
however, to recognize that the amount of carbon pigment
on the surface does not necessarily indicate the extent or
distribution of the pigment in any part of the lung tissue.
There are factors arising with each lung and within each
lobe which tend to modify the amount of pigment within
the tissue.

Although the pigment follows the septa of the lung
lobules, the distribution upon the surface is by no means
uniform. It has been repeatedly observed that the amount
of pigment in the different lobes as well as in the different
portions of the same lobe varies very considerably. The
distribution of the pigment in the sub-pleural tissues is
dependent upon the course of the lymphatic stream. But,
as has been indicated by S. R. Haythorn, the presence of
carbon pigment within the lung may have a marked effect
upon the subsequent condition of these lymphatics. Thus,
as we shall discuss later, the deposition of carbon pigment
resulting through the activity of certain phagocytic cells

has a tendency to stimulate tissue changes which modify the architecture of the organ. It is most probable that by this means the deposit occurring in the lung tissue does not always appear in the same characters, but according to the particular tissue reaction (fibrosis) a modification of the lymphatic system leads to an altered physiological process in which the amount of deposit may be increased or decreased.

In the examination of a series of lungs it soon becomes evident that there are certain areas in the normal organ, which become involved earlier than others, and which usually show the most intense pigmentation in the later stages of the process. Thus in young adults, who show no evidence of other disease processes in the lung, the pigment is more prominent in the apex of the upper lobe, the anterior border of the upper lobe, and the posterior border of the upper and lower lobes. Even in these three areas the distribution of the pigment is by no means uniform, for in different individuals the grades of intensity of the deposit differ somewhat within these locations.

It is the usual observation that the least pigmented portions of the pleural surface of the lung are the diaphragmatic and the interlobar surfaces. It is not uncommon, however, to observe a sharp line of pigmentation separating the outer surfaces of the pleura from the interlobar areas. At the border of each lobe as it lies in apposition to its fellow, there is a marked pigmented zone, more intense than the deposit upon the free surface, and serving as a boundary between the pigmented pleura and the non-pigmented interlobar surfaces.

The distribution of pigment in the apex of the lung varies according to the shape of the part and to the character of the dome of the chest cavity. As has been pointed out by Schmorl it is not uncommon to have an unusual prominence of the upper ribs and irregular folds of the parietal pleura forming bands which divide the otherwise round dome of the chest cavity into several smaller compartments. These abnormal ridges are very common, but are not constant in their disposition. Not uncommonly

they pass from behind inwards and forwards, crossing the dome in an arched and rather spiral direction, the anterior extremity passing towards the hilus of the lung. At other times, folds of parietal pleura pass from behind upwards and forwards, crossing the highest points of the pleural sac. When these folds are marked a definite depression is left upon the lung surface, particularly if the lung is unduly distended by emphysema or pneumonia. This depression is observed in the nature of a groove looking not unlike the vertical grooves seen over the right lobe of the liver (Liebermeister's groove). These grooves become more marked and more permanent with the age of the individual. Not only do they present depressions in the soft and spongy tissues of the organ, which, in the early years of life, can easily be obliterated, but in the course of years they remain as definite areas of retraction where the lung substance does not expand nor develop equally with the rest of the tissue. Thus in the apical grooves the lung tissue is inhibited in its growth and its functional activity is hindered by obstructing bands. Moreover, the lung tissue opposite the depths of the grooves is prone to become fibrosed or to develop adhesions to the parietal pleura.

These apical grooves are also to be recognized in the variation of the deposit of the pigment. The grooves when well marked attract the attention by showing a lessened amount of pigment than the surrounding tissue. When several well marked grooves occupy the apex of the lung, then this part of the lobe appears to contain decidedly less pigment than other parts. Yet on closer examination, although the apical pleura may appear to contain less pigment than the other pleural areas, this is due to the absence of pigment in the grooves themselves, and not to the variation of pigment in the parenchyma of the lobe.

The ridges bounding these grooves usually show an unusual pigmentation. The extent, however, of the deposit on the borders of the grooves, is not uniform in that it is not uncommon to observe one border deeply pig-

mented while its fellow on the opposite side contains but little carbon.

The intensity of the pigmentation along the posterior border of the upper and lower lobes is commonly the most marked in the entire organ. From the early beginning of a tortoise shell marking indicating the division of the lobules, the condition progresses until the pigmentation produces one diffuse coloration of the pleural tissues.

Furthermore, there are two important considerations respecting the localization of anthracotic pigment in the pleura. The first of these is the relation of the pigment deposit to the position of the intercostal spaces and the ribs. The second is the relation of the pigment deposit to the opposed pleural surfaces between the neighboring lobes.

In respect to the relation of the pigment to the ribs and intercostal spaces there have been a number of views expressed. As above stated, our attention has been particularly attracted to this question through the observations of Schmorl upon the apical grooves of the lung. Similar rib impressions are found in adults upon the surfaces of both the upper and lower lobes. Schmorl in 1901 indicated that the uppermost ribs produced individual impressions upon the lung substance which were easily recognized at autopsy. Schmorl found these depressions in children, but noted that they tended to disappear with advancing age. He believed that the depressions were the result of the undeveloped chest pressing upon the lung substance and that with the development of the thorax, in the normal individual, the pressure upon the lung was much relieved. He noted, however, that in those individuals, whom we are prone to look upon as possessing the anatomical character of a tuberculous subject, the flat chest, these grooves or rib depressions upon the lung remained permanently. Thus he believed that the anatomical characteristics of the chest altered the relationship of the lung to the pleural cavity which in the undeveloped condition was prone to bring about those anatomical changes of the lung, inviting tuberculosis.

The grooves in the lung tissue had the effect of compressing both the lymphatic and blood vessels. Likewise a certain interference might be produced in compression of the bronchial tree. These pathological conditions tended towards a stasis of the circulation of the part, permitting a more ready development of the tuberculous process.

It has, furthermore, been shown that not only do the ribs in the uppermost portion of the thorax leave their impression on the lung tissue, but that such marks may be distinguished for the entire series of ribs down to the eight or ninth. These rib markings or impressions are more readily followed by observing the deposit of pigment than by the actual depressions produced upon the lung substance.

As one will readily appreciate, the intensity of the impressions of the ribs upon the lung varies in different individuals. Not uncommonly, the thorax is of such dimensions or its capacity bears such a relation to the lung, that little or no effect of rib pressure is to be noted. Under those conditions in which the volume and consistence of the lung is increased, as in lobar pneumonia, the rib depressions are temporarily more decidedly marked.

Peiser has studied a series of cases and finds that the rib grooves are not well marked in the infant. In this he differs from Schmorl. He believes that the rib grooves increases in their depth as the individual assumes the upright position and the thoracic wall sinks. As the thorax, with increasing age, gradually assumes its new level, the upper ribs become more prominent on the inner wall of the thorax. These then produce depressions upon the lung surface. Not only does the sinking of the thoracic wall lead to the prominence of the rib margins, but the respiratory movements are altered, there being a diminished respiratory activity established. This in its turn has the effect of producing a pulmonary stasis and a lessened elasticity of the lung. Peiser believes that with the altered condition of the respiration, the character of the lung sub-

stance changes so that the rib grooves are more readily produced.

Further observations have recently been made by Orsos. He studied the mechanics of respiration as regards the relationship of the expanding thoracic wall to the spongy lung substance within. He indicates that the thorax, constituting a closed cavity, has its walls made up of parts which are of different composition. In part, the wall consists of solid structures, the ribs, while in other places soft portions, make up a part of the active walls. He points out that the effect of these two types of tissue upon the lung substance is different. The solid ribs, he believes, are more active in producing a suction by the expanding chest and a compression by the contracting chest wall. This greater activity in relation to a part of the chest wall has its effect upon the lung substance in that the tissue immediately opposite the firm ribs is functionally more active during the respiratory movements. The inactivity of the intercostal spaces is not only to be observed in the smaller alveolar spaces, but also in the more sluggish lymphatic drainage leading to the greater deposition of the insoluble carbon particles. Thus in the adult the intercostal spaces become more richly marked by the deposit of anthracotic materials.

In discussing the views expressed by Orsos, an opposite stand was taken by Marchand, Aschoff and Beitzke, in that each of them expressed his belief that the greater deposit of pigment occurred in the areas mapped out by the ribs.

In our own observations, we must, in the main, agree with the findings of Orsos. Some difficulty is experienced in determining which portion of the lung lay opposite the ribs, particularly when there have been no marked depressions, while the deposit of pigment is quite decided. There can, however, be no doubt, as to the depressions opposite the first, second, or third rib, and in these situations, the grooves which are very decided contain less pigment than the high points of the ridges. At this point, however, it is necessary to introduce a word of explana-

tion in discussion of the pigment deposit in and about the costal grooves. It is best to study those lungs which are moderately advanced in the anthracotic process, and which are not altered by the presence of adhesions. Inflammation introduces a factor which modifies the normal distribution of pigment so that we can no longer ascribe our findings to the influence of the costal grooves alone. We shall discuss the effect of inflammation upon the deposit of coal pigment at another place.

It is, furthermore, to be indicated, that the deposit of pigment along the intercostal areas is not uniform. Although the margins of the grooves as well as the intercostal spaces contain the greater amount of the pigment while the depth of the groove is almost always free, it is impossible to make a common statement as to the exact outline of the deposit for each groove. No doubt, the intensity of the pigmentation is determined to a certain extent, by the individual characters, such as the prominence of the ribs, the corresponding depth of the groove, and the local pressure upon the lymph and blood vessels.

In support of the views of Orsos that the cavity of the grooves exhibit less pigmentation than the surrounding portions, is the fact that the natural depression as well as the opposed pleural surfaces between the lobes have the same characters as the rib grooves in being less pigmented than other parts. It is the common observation to find a pale non-pigmented pleura on the interlobar surfaces while the external visceral pleura is mottled by a pigment deposit. The same is true of the diaphragmatic surface. Here, too, a less amount of pigment accumulates. This variation in the distribution of the pigment upon the pleural surfaces is not dependent upon the difference of the respiratory function of the lung alveoli beneath these parts, nor is it due to a difference in the character of the distribution of the lymphatic channels which surround the lung alveoli, but it is dependent upon outer influences of pressure which modify the capacity both of the alveoli and lymphatics. In the normal lung these influences of pressure are to be observed mainly in the rib grooves, the

interlobar and diaphragmatic surfaces. It is possible that the presence of points of pressure upon the lung tissue has the quality of massaging the parts during respiratory activity and thus driving the particles of pigment more rapidly to other parts. We are inclined to believe that this quality of massaging the part by intermittent friction, plays the important role of preventing the accumulation of carbon pigment in the given regions of the lung. As we shall point out later, the lack of flow in the lymphatic system does not prevent the accumulation of foreign particles. Stasis of the lymphatic system, although preventing the fluid within the channels from flowing with normal rapidity has little effect upon the migration of the cellular elements, which are the main means by which the foreign material is transported. Thus, although stasis prevents the proper flow of the serum through the lymph channels it permits the wandering of phagocytes into the obstructed region where these may accumulate in undue proportion. These wandering cells with their pigment burden are the chief causes for the pigmentation of the given areas of lung tissue.

INTERSTITIAL PULMONARY ANTHRACOSIS.

The nature of the distribution of carbon pigment in relation to the pulmonary alveoli within the lung is very similar to that observed upon the pleural surface. We do not, however, have an opportunity of viewing the pigment in the same manner. Thus in a cross section of the lung we do not have the opportunity of observing the surface of the lobules, but see only cross sections of the partitions. Thus for the most part our attention is attracted to the deposition of pigment at the points where the partitions meet. In these situations we observe small nodular deposits not uncommonly the size of pin heads. At first sight, it would appear that the amount of pigment within the lung is relatively less than that observed on the surface. Nevertheless, it can be observed that the total amount of pigment within the lung tissue bears a rela-

tion to the quantity observed on the surface. In the normal lung, however, the distribution within the tissue is more uniform than the distribution of carbon in the pleura and there is not the macroscopic variation in different parts of the lobes, save at the hilus where the parenchyma is more pigmented on account of the greater accumulation in small lymphatic channels and nodes.

Furthermore, the unequal distribution of the pigment as it is observed upon the pleural surface has no direct relation to the deposition within the organ. The lack of pigment upon the interlobar surfaces and in the rib grooves is only a superficial condition and does not affect the deeper underlying lobules. The earliest deposits of coal pigment are to be looked for mainly in the perivascular lymphatics of the smaller branches of the pulmonary artery, subsequently, pigment appears in the regions of the small bronchi and venules. In all of these situations its presence becomes more marked with the increasing quantities of soot that are constantly inhaled.

As the accumulations of pigment gradually increase, they not only form lines along the septa of the lobules and the vascular channels, but nodular collections appear at the points of junction of the various lymph channels, where small receptacula are formed. These nodules becomes so prominent that they are readily felt by the finger and at times the course of the lymph channel can be detected by the feel.

Tissue changes may or may not accompany these larger depositions of pigment. In the majority of instances, however, a process of fibrosis, not accompanied by any inflammatory exudate, makes its appearance and surrounds each pigmentary nodule. These can be detected by the naked eye, while the larger ones, which are shot-like and gritty, are commonly spoken of as "anthracotic nodules."

In none of our specimens were we able to observe any uniform variation in the deposit of the anthracotic pigment within the lung of normal individuals. The greater quantity of pigment along the various channels has been

indicated above, but no unequal distribution of pigment has been observed which would in any way correspond to the unequal distribution beneath the pleura. True it is, however, that certain pathological processes in the lung tissue may modify the distribution of the pigment to a very great degee. We have, however, failed to find any evidence of excessive deposit in the deep tissues at the apex of the upper lobe. In fact, in our experience more pigment was found toward the hilus than at the periphery, regardless of the pleural distribution. Furthermore, the more marked areas of pigment deposit in the pleura are confined to this superficial layer and do not involve the underlying parts.

In several specimens of lungs from elderly individuals, who showed a moderate amount of emphysema in portions of the lobes near the surface, it was observed that an unequal distribution of the anthracotic pigment was present. Those lobules showing emphysema contained less pigment than elsewhere. This condition was not only apparent by the greater area occupied by the emphysematous tissues, but was real, in indicating less carbon in the affected tissues. When such emphysematous areas occupy the surface alveoli and when these lie upon the ridges of the costal markings, it is then found that the borders of the grooves contain less pigment than the surrounding areas. Thus the contention of Marchand and others that the ridges between the intercostal grooves accumulate less pigment may have its explanation in the presence of these emphysematous alveoli.

THE MODIFICATION OF ANTHRACOTIC DEPOSITS BY OTHER FACTORS.

It is evident from what we have said, that every individual has a greater or less quantity of carbon accumulate in the lungs, and that this accumulation varies in the normal lung according to the amount of carbon in the inspired air. With advancing age, the quantity of pigment continues to increase until a relative standard for

the community in which he resides is reached. This pigment in the normal lung becomes deposited, through the agency of phagocytic cells, within the lymphatics and its particular location beneath the pleura of the lung, is dependent upon the distribution of the lymph channels and the relationship of the opposed pleural surfaces which varies to some extent in all individuals. The distribution within the normal lung substance appears to be entirely determined by the circulation within the lymphatics.

Whereas under normal conditions we may look for certain common features in the anthracotic deposits in the lungs, there are also pathological processes which bring about a modification of the deposit. Thus we find that certain disturbances within the lung tissue have an effect of inducing greater deposits of pigment within localized areas. And it is probable that this new condition of excessive pigment deposit brings about further changes instituting a vicious circle.

A. LOCAL PLEURAL INFLAMMATION.

It is not an infrequent observation to find a greater quantity of pigment in the immediate vicinity of a band of pleural adhesions. By some it has been suggested that these adhesions are the result of the unusual deposit which leads to an excessive irritation in the surrounding tissues. When, however, we study the development of pleural adhesions we find that the fibrous bands in children show little or no difference in the deposit of pigment from other parts of the lung. With advancing age, however, the accumulation of carbon at the point of attachment of the adhesion to the lung becomes greater. A difference is noted, too, in the character of the adhesions, for those which have only a superficial attachment and do not induce a fibrosis of the neighboring lung tissue, show less deposit. It is obvious that we must differentiate those pigmentary processes associated with primary pleural adhesions from those that we associated with primary lung

disturbances (tuberculosis), in which adhesions may also be present. Of this latter type, we shall speak again.

The best example of pleural adhesions for study are those developing between two surfaces which are in constant frictional contact, as well as the bands of adhesions which sometimes follow fibrinous pleurisy in early life. Of the former type we meet with adhesions at the apex arising from a rib groove which, under ordinary circumstances, is non-pigmented. Here a firm band of adhesion binds a portion of the lung to the chest wall. The fibrous band not alone attaches itself to the surface of the visceral pleura but bands of tissue enter to a greater or lesser extent the fibrous layer of the lung covering and the interstitial septa, and alveolar walls. The fibrosis spreads diffusely through the tissue surrounding the blood vessels and encroaches upon the loose tissue of the lymphatics. Some of the lymph channels become completely obliterated, others are altered in their course.

It is probable that some of these bands of adhesions develop without the presence of an acute process and like the presence of milk spots of the heart, induce a progressive fibrosis which alters the relationship of the surrounding tissues. The pleura with its vascular tissues is altered to a sclerosed structure in which the lymph channels are reduced to mere clefts. In this condition not only is there a stasis of the fluid within these channels, but there is also a filtering out of the phagocytic cells which are constantly wandering from the alveoli towards the larger lymphatic system at the hilus. Gradually the accumulation of cells is sufficient to show the increased quantity of pigment within the part. It would appear according to Haythorn, that these migrating cells may live for a considerable period with the pigment within their protoplasm. Other phagocytes probably liberate their contents which become deposited in the interstices of the fibrosed areas. It is probable that the liberated carbon remains in the clefts between the cells and does not enter fixed tissue cells.

If the opportunity for the absorption of carbon pigment from the alveoli be great, then the accumulation of this foreign material in the vicinity of adhesions becomes very marked. Nodules are formed which are hard and encroach upon the lung tissue. The lung alveoli are surrounded by a progressive fibrosis containing much carbon. It is more than probable, that when such excessive quantities of pigment are deposited that these again act as irritants, inducing greater adhesions. We do not believe that the inhalation of carbon in the normal lung will induce pleural adhesions unless some other factor within or upon the lung acts as a primary exciting cause. We have upon repeated occasions observed the lungs of mill workers and coal miners in whom the lung tissue had become intensely black through carbon deposit without there being any evidence of pleural adhesions.

We have never observed acute pleurisy to alter the deposit of pigment in the pleura. It has been observed that in acute inflammatory processes where the lymphatic channels of the pleura are filled with migrating and phagocytic cells that a considerable amount of pigment may be removed from the pleura to other parts. The exact bearing which this inflammatory migration might have upon the total pigment content could not be determined. The changes, however, were insufficient to produce any difference in the amount of pigment to be noted by the naked eye.

On the other hand, the chronic processes of the pleura not uncommonly had an effect similar to that observed associated with individual tags of adhesions. In cases where there were universal fibrous adhesions, the effect was not observed in the quantity of pigment deposit except where denser bands had developed. The diffuse and veil-like adhesions were without change in the vicinity of their attachment to the lung. A study of these indicated that the fibrous tissue of these adhesions had only a superficial attachment and did not involve the deep layer of the pleura. Where, however, the intensity of the chronic adhesive pleurisy was not uniform and where irregular bands

were attached to the lung substance at various points, here a more marked pigment deposit was prone to form.

In all instances where the more intense deposit of carbon pigment was associated with bands of adhesions, the process remained fairly superficial and localized. There was no invasion of the deeper parts by the continuous accumulation of pigment.

B. INFLAMMATION OF THE LUNG SUBSTANCE.

Much has been indicated to associate pneumokoniosis with acute and chronic respiratory diseases. As early as 1717, Ramazzini drew attention to certain air borne occupational diseases, and since then the greatest attention has been paid to diseases associated with inhalation of dust. Naturally, much interest has centered about the effect of inhaled dust of various kinds upon the lung and more particularly the relation, if any, that existed between these changes brought about by the deposits and inflammatory processes induced by bacteria. The manner in which this relationship was established has not been entirely clear. By many (Ascher and others), however, tuberculosis has been looked upon as a process secondary to the deposition of the dust.

On the other hand, the relative infrequency of pulmonary tuberculosis amongst those who are engaged in work associated with much coal dust, has been pointed out by a number of authors (Ogle, Sommerfeld, Hirt). In the statistics, tuberculosis appears rather rare among coal miners. It would, therefore, appear that the inhalation of coal dust does not predispose to tuberculosis. The explanation for this appears to depend upon the morphological characters of the dust particles. On the other hand, Kuborn, Villaret, Versois, and others believe that the continued contact with coal dust leads to a true immunity against tuberculosis. Racine believed that coal contains substances which are antiseptic and disinfectant and that this quality inhibits the growth of the tubercle bacilli, and Holman has shown similar disinfectant qualities in

soot. Another (Idel) believed that the porous coal dust absorbed the tubercle bacilli and rendered them inert, while Wainwright and Nichols thought the partially soluble calcium salts contained within the coal gave the animal body protection against these organisms. The indication that the presence of coal dust within lungs had a favorable effect upon respiratory diseases, led Guillot to use the inhalation of coal dust for therapeutic purposes. As early as 1793 Beddoes established a sanitarium near Bristol where he treated chronic diseases, as asthma and consumption by the inhalation of charcoal. The patients were placed in a dusting box where by mechanical means the charcoal was distributed into the air. However, it was later shown by Papasotiriu that coal dust had no influence upon the growth of the tubercle bacilli upon glycerine agar cultures, while Cornet was unable to protect animals against air borne tuberculosis by means of the inhalation of carbon dust. It has been indicated by Bartel and Neuman that anthracosis increases the virulence of tuberculosis in experimental animal infection.

It is more than probable that the infrequent presence of tuberculosis amongst those developing extensive anthracosis has its explanation in certain anatomical changes in the respiratory system and it is possible, as is indicated by Fraenkel and admitted by Racine, Wainwright and Nichols, that the infrequence of progressive tuberculosis among the coal miners is due to tissue obstruction of the lymphatic channels brought about by the anthracosis.

Ascher's observations that the extensive inhalation of smoke as well as soft coal increases the mortality in tuberculosis, is not in agreement with other general findings. It has, however, been shown by Hart that there is a difference in the composition of smoke particles and coal dust, and that the former contains some of the products of coal distillation. Again it has been shown by others that laborers engaged in atmospheres containing much coal dust, such as stokers, coal heavers, and chimney sweeps, are just as immune as coal miners to tuberculosis (Markel, Versois). Lewin found that 92.3 per cent. of chimney sweeps

who had followed this occupation for more than 10 years were free from respiratory diseases.

Our own observations have concerned themselves in determining the influence of the pigment upon the lung tissue as well as its relation to the tissue changes in acute and chronic processes within the lung. We can offer no statistics which show the relation which the pigment deposit has to the occurrence of infections of the lung. This study also deals with the effect of certain respiratory diseases upon the subsequent deposition of carbon pigment.

As it has been shown that the anthracotic material owes its presence to the activity of certain phagocytic cells it is evident that an interesting problem confronts us in determining what role similar cells stirred to activity by a bacterial irritant will have upon the foreign materials, as carbon pigment, which are already present in the interstitial tissues.

In the study of lung tissues showing acute pneumonia one is confronted with the picture of a lesser pigmentation in the areas involved in the pneumonia. The appearance is quite decided and a fairly sharp line of demarcation separates the pneumonic area from the more healthy tissues. Within the consolidated portion of the lung the carbon pigment is seen only in the more prominent nodular deposits while the pigment observed along the interlobular septa in the normal lung can no longer be traced. The diffuse pigmentary deposit in the alveolar walls is also overshadowed by the color of the exudate, be this grey or red. However, when viewing the lung from its pleural surface no change in the amount of pigment deposit is observed in the superficial portions.

Although a decided diminution of pigment within the consolidated area is apparent, the fact that pigment is actually removed from the tissue involved in the inflammatory process can not be demonstrated in the lung after its recovery from pneumonia. We have not been able to define the areas of consolidation after recovery from the disease, by the amount of pigment in the tissues.

It does seem, however, that some of the pigment in the lung tissue becomes dislodged during the active migration of cells. During the late stages of pneumonia, the lymphatic channels contain a greater number of pigment bearing cells than are observed in the uninvolved lung. It may be that, due to the stagnation of the lymphatic system in anthracosis, these pigment bearing cells do not have an opportunity of migrating from the pulmonary structures, but remain stagnant in the dilated lymph channels. The macroscopic appearances of a diminution of carbon pigment during the acute stages of the pneumonic process is more apparent than real and is due to the overshadowing of the normal lung structures by the cellular exudate of the inflammation.

On the other hand, we have repeatedly observed that in isolated areas of fibrosis of the lung where no evidence of tuberculosis was found that the amount of anthracotic pigment was much increased over that present elsewhere in the same lung. We can, however, hardly offer this as an indication that the sequel to an acute inflammatory process, ending in fibrosis is associated with an excessive pigmentary deposit. In a single case of well advanced organized pneumonia we observed some increase in the amount of macroscopic pigmentation within the fibrosed area as well as microscopic evidence of such increased deposit. Naturally, it is difficult to estimate the exact variations from the normal deposit in different parts of the same lung.

In no instance has the examination of pneumonic lungs shown that the presence of the anthracotic deposit has in any way modified the distribution of the acute process. It can not be shown that the more intensely pigmented tissues are more readily subject to pneumonia than the other less involved areas. It has, however, been suggested by Haythorn that aside from the local pigmentation in the vicinity of the individual air sacs, the anthracotic process of the lung has a definite effect upon the lymphatic system and particularly the lymphatic channels. These channels, which become narrowed and partly obstructed,

are less efficient for carrying off the debris which accumulates in the acute inflammatory process. This stagnation impairs the process of resolution with the result that proper repair of the lung following pneumonia does not take place. Conditions of unresolved pneumonia and gangrene of lung are more common in lungs with marked anthracosis than in the less affected organs.

We have in many examples made observations upon the anatomical relationship between the anthracotic deposit and tuberculosis. It is immediately apparent that in the discussion of such a relationship we must clearly define the type of tuberculosis. Naturally, the effect of the distribution of the tuberculous process upon the anthracotic deposit will be different in acute miliary tuberculosis than in chronic localized tuberculous lesions, and similarly the reverse relationship, if such exists, will also differ with the various forms in which one meets the tuberculous process. Individually both processes are dependent, for their local distribution, upon similar factors, the phagocytic activity of cells and the distribution of the lymphatics.

We have not been able to observe any direct bearing of the anthracotic process upon acute miliary tuberculosis, nor have we observed a greater tendency for the development of tuberculous lesions in the anthracotic areas than in other parts of the lung. In fact, lungs showing moderate anthracosis will have more acute miliary tubercles in the uninvolved portions of the lung than in the anthracotic nodules. Nevertheless, we have observed that in the later stages of the process when the miliary tubercles had advanced to larger and more definite caseating areas that the localized areas of anthracosis not infrequently had gray tuberculous centers. It is probable, therefore, that the absence of tubercles within anthracotic nodules during the acute stage of the infection is, in part, due to the intense pigmentation obliterating the early tuberculous focus. As the anthracotic deposit is associated directly with the course of the lymphatic streams and particularly with those surrounding the blood vessels, it is to be ex-

pected from what we know of the distribution of tubercu-
losis that many tubercles will develop along these systems,
in spite of the presence of anthracosis. As the individual
miliary tuberculous foci increase in size they gradually
obliterate the anthracotic areas with the change from an
intensely pigmented tissue to one showing numerous gray
nodules of various sizes. With the increase in number, the
tissue gradually loses the intensity of its pigmented ap-
pearance.

A still more marked loss of anthracotic pigment from
the lung is seen in caseous pneumonia. Here, instead of
having many small gray nodules gradually obliterating
the pigment within the lung, we observe a diffuse gray
caseous tissue whose light color is in strong contrast to
the pigment in other portions of the lung. Only a mod-
erate amount of pigment deposit is seen in the caseous
area, and this pigment lies in the areas of former intense
deposit. The gray color of the caseous areas not only
represents the necrotic exudate within the alveoli, but also
indicates tissue changes, first proliferative, later degener-
ative of the alveolar walls, and their contents. It is during
the process of proliferation in the alveolar walls and lung
trabeculae that the former pigmented cells are stimulated
to proliferation and probably migration, which leads to a
removal of the pigment in the particular area. What
eventually becomes of the disturbed pigment in the lung
tissue during the tuberculous process is difficult to say.
In part, it finds its way towards the lymphatics at the hilus
of the lung. In part, it may become removed by the de-
struction of the tissue and subsequent expectoration.

In the above processes, acute miliary tuberculosis and
caseous pneumonia, it is evident that the anthracotic
process has no influence in localizing the infection. We
have, however, observed that miliary tuberculosis is more
prone to develop into a chronic caseous miliary form in
lungs presenting much pigmentation than in those not af-
fected.

Quite a different outcome is observed in localized
chronic caseous tuberculous foci. The early stages of the

tuberculous process simulates the lesions which we have just described. As the lesion enters the chronic stage one observes that instead of there being a diminution of pigment in the involved area that gradually and in direct proportion to the amount of fibrosis the pigment deposit increases. Thus the periphery of the lesion in which area the healing of the tuberculous mass is taking place, larger amounts of pigment are continuously laid down. We have never observed the macroscopic increase of pigment before the development of fibrosis in the tuberculous lesion. Eventually the fibrosed mass becomes intensely black and hard. These areas vary in size from a pea to a mass the size of a golf ball. When fully developed the tissue with its pigment deposit resembles in consistance and color a hard rubber ball.

We have observed all stages of these pigmented masses surrounding tuberculous foci and it is evident that the pigment deposit develops upon the tuberculous lesion. The extent of the pigmented area is entirely dependent upon the reaction in the tissue of the tuberculous focus, and this reaction is always of the development of fibrosis. Where a tuberculous process by progressive caseation has lead to cavity formation there is no excessive pigmentation in the vicinity of the cavity until repair by fibrosis has begun in its walls.

Microscopically, it has been shown that the same cells, which form the tubercle and which in themselves are phagocytic for tubercle bacilli, are also the cells most phagocytic for carbon pigment. Thus these cells, constituting the tubercle, are adapted for the localization of foreign dust particles, and being in excess of the number present in the normal parts of the lung, may bring about an anthracotic deposit, with the tubercle. However, by the time the pigment has accumulated in sufficiently large quantities to be recognized macroscopically, there has developed a secondary fibrosis inducing a vicious circle by obstructing new lymphatics and accumulating greater numbers of pigment laden cells.

TISSUE CHANGES INDUCED BY CARBON PIG-MENT WITHIN THE LUNG.

To-day we have come to recognize that the term anthracosis does not refer alone to the presence of coal pigment within the lung, but also includes the tissue changes which accompany this deposit. As we have previously indicated we have come to recognize that the deposition of the carbon in the lung is brought about through the agency of phagocytic cells. It is not probable that inert carbon can enter the lung tissues by mechanical means alone. The contention of Klein, Sikorsky, Merkel and others that the physical characters of the foreign material is such that it may migrate between the cells in the alveolar walls without the assistance of wandering cells can no longer be supported. Hence it is evident that the very process of accumulating and carrying the pigment is a vital one and has to do with the cells arising from the pulmonary tissues. It has been shown that the number of cells acting as phagocytes found within the alveoli is proportionate to the quantity of pigment in the air sac and thus, too, the activity of the wandering cells is dependent upon the inhaled carbon. As the engulfed pigment is prone to remain fixed for considerable periods of time, it even being claimed by some that the phagocyted pigment remains permanently within the wandering cells, there is a progressive accumulation of these cells in the lymph spaces of the alveolar walls. Their direction is mainly towards the larger lymphatic system at the hilus of the lung, but it is also probable that these cells may not only lie inactive for varying periods of time, within the interstitial lymph spaces, but are still capable of returning to the air sacs to encumber themselves with still more foreign material.

How long these cells of an endothelial type are able to remain dormant but still living, is very difficult to say, yet it has been demonstrated in tissues that pigmented cells having every appearance of fixed connective tissue

when thoroughly analyzed and segregated from their surroundings were found to be endothelial cells.

It is the common observation to find a progressive accumulation of pigment bearing cells within the alveolar walls with advancing ages. As the cells increase in number within the lymph spaces the wall becomes thicker and the tissue has a more or less hyaline appearance between the aggregations of pigment granules. To a certain extent the increase in tissue is the result of a direct increase in the number of wandering cells. On the other hand, we have also been able to show that there is a definite increase in the connective tissues about the lymph channels with the laying down of heavy collagen strands.

With this fibrosis there is no increase in the elastic tissue, in fact, the areas of extensive change are poorer in elastic fibers than normal.

As we have previously indicated the distribution of the inhaled dust in the lung is quite uniform, save for its distribution in the lymphatics of the pleura. Some (Arnold and also Boer) maintain that the deposition of soot is considerably greater in the upper lobe. This has not been our finding, though at times a difference has been observed between the two lungs. The accumulation of dust to that extent which induces secondary fibrosis will thus give rise to a fairly uniform tissue change in all lobes of the lung. This is a common finding in as far as the lung tissue proper is concerned. It is probable that the fibrosis thus produced assists further with preventing a proper lymphatic circulation (Haythorn) and leads to the greater number of phagocytic cells becoming localized in the alveolar walls.

It is probable that the very nature of the phagocytic cells, being large and sluggish in activity, leads to their more ready localization in the lymph clefts than the more active leucocytes which deal with acute disturbances. If the normal functions of the endothelial phagocytic cells would be continuously carried out, it is improbable that as great a quantity of carbon would localize in the parenchymatous tissue of the lung, more of it finding its way

to the large lymphatics and lymph glands at the hilus. The very condition which is brought about by the obstruction of the lymph clefts and small channels as well as the blocking of the lymph sinuses in the nodes about the bronchi tends to increase the localization of the large phagocytes close to the alveoli from which they obtain their pigment. Thus the nature of the pigment phagocytosis and the localization within the lymphatic spaces tends to bring about a vicious circle which, when a certain degree of anthracosis has developed, permits of a still more rapid deposit of pigment in the alveolar walls. It is about in this stage of the condition that the developing fibrosis leads to structural changes which impair the function of the lung tissue.

Other than inducing a diffuse fibrosis within the lung, there are also the nodular fibrotic masses surrounding accumulations of pigment and pigment bearing cells at the junction of the lymphatic channels. The more common of these are the size of wheat grains. The fibrosis assumes a concentric arrangement enclosing pigment which to a great extent lies free but much of which is contained in the original phagocytic elements. Such nodules, however, may become much larger, forming isolated masses, three or four cms. in diameter. It is probable, however, that these larger masses arising in the lung tissue have had other factors superadded, leading to their unusual development. The consistence of these is that of hard black rubber. Where calcareous masses are found in the center of such nodules, the previous existence of tuberculosis is strongly suggested. This association of anthracosis with chronic tuberculosis we have discussed above.

ANTHRACOSIS AND EMPHYSEMA.

With extensive and diffuse development of pulmonary anthracosis in which tissue changes to a greater or less degree are developing, the activity of certain parts of the lung is impaired to such a degree that compensatory changes occur in other and more active parts. These com-

pensatory changes are mainly evidenced in the development of emphysema. It would be difficult to indicate the sequence of events in laborers or coal miners. Here, from the very nature of their work emphysema would readily occur. We may, however, observe emphysema in individuals with diffuse anthracosis whose work or whose thoracic condition would offer no explanation, for the compensatory expansion of certain lung areas. This we have on several occasions observed and we were unable to find an explanation save in the diminished functional activity in those portions of the lung with marked anthracosis and fibrosis. The development of the emphysema observed in the positions is seen under other conditions.

The apex and the anterior border of the upper lobe are usually most involved. A rather remarkable feature associated with this emphysema is the disappearance of the anthracotic pigment from the emphysematous area. Where the alveoli become usually distended the pigment gradually disappears until the tissues look quite white (pulmonary albinis). This has been commented upon by Beitzke and others.

From our observations it would appear that this loss of pigment from the lung is the result of the greater local activity during the process of development of the emphysematous areas. The condition would simulate the lack of pigment observed in the interlobar pleura where the massage of these areas by constant friction seems to drive the pigment bearing cells into the larger lymphatics. This is probably also the case during the development of the emphysema where the lung alveoli are acted upon by the greater air pressure having the effect of repeated compression and relaxation. Thus the air contained within the alveoli has the effect of massaging the alveolar walls and likewise of driving onward the cells containing the pigment. A similar effect would also be had upon the free pigment within the lymphatic spaces of the alveolar wall. In these emphaysematous areas the removal of the pigment is not associated with an inflammatory process assisted by leucocytic phagocytes.

QUANTITATIVE ESTIMATION OF CARBON IN LUNG.

As we have indicated, a fair estimate for comparison can be made of the carbon deposit by the naked eye appearance. The pleural deposit of carbon, although not directly related to the presence of pigment in the inner portions of the lung, is, nevertheless, a good guide to the quantity of foreign material in the organ. The pale gray or grayish-pink color of the lung of the rural inhabitant is readily distinguished from the mottle, streaked or slaty black tissues of the city dweller. Moreover, as we have indicated, the progressive increase of the carbon deposit, in the lungs of every citizen in manufacturing communities, can be recognized and grouped into the age periods by decades, when the individual has lived fairly constantly in the same district. Individuals of similar occupation are exposed to relatively equal amounts of atmospheric carbon, and their respiratory tissues receive similar quantities of carbon by inhalation. On the other hand, in communities where within short ranges of distance the atmospheric conditions differ, and with this the carbon content of the air is very unequal, the peoples living or working but short distances apart are subjected to diverse conditions, the one inhaling much larger quantities of soot than the other.

There are so many factors associated with the deposit of soot in the lungs of human individuals that it is impossible to make any general statement indicating the amounts for each. In truth, it is plain that those in smoky atmospheres have larger deposits, but we are often misled in our reference as to occupational influence. The millworker employed within the sheds in the manufacture of steel is often less exposed than his wife living within a quarter-mile range enveloped by the smoke clouds from the multitudinous stacks. The lungs of a peddler selling his wares to the foreign population of our smoke-laden valleys

were found to contain more carbon than those of the mill-hand (see table below).

As we feel convinced from our observations, that the intestinal route has little or no practical significance for the deposit of carbon in the lungs, it does not appear that the degree of cleanliness—particularly of the mouth—bears any relation to pulmonary anthracosis. Carbon particles once lodging upon the moist surfaces of the nose, mouth, pharynx and trachea, never assist in increasing the carbon of the lung. It is probable, as was shown by Haythorn's experiments, that only those carbon particles lying within the alveolar sacs can reach a permanent interstitial abode and that little if any carbon is phagocyted and carried into the tissues from the bronchi or bronchioles. Furthermore, it would appear, both from experimental and other observations, that the carbon reaching the lung alveoli is only a very small portion of the carbon content of the air as inspired, and this portion has reached the lung because it escaped contact with the moist mucous surfaces of the respiratory tract. Under the most trying circumstances of a smoky atmosphere we are amply protected by the sticky surfaces of tortuous tubes.

Difficult as it seems for carbon to reach the lungs, it appears equally difficult to dislodge the pigment when once it has been incorporated by the tissues. In fact, we may well believe that, save under very abnormal circumstances, carbon once within lung tissue remains for life, and hence each year we add that amount to our store as we may have been exposed to city smokes. To gain some accurate information of the quantitative deposit of carbon in the lungs an analysis was made of the tissues. Previous analyses have been made determining the quantity of iron, silicate, copper and other metalic deposits in the lungs of laborers.

Saito in a series of experiments estimated the quantity of dust inhaled from the air. Using measured quantities of dust (white lead) he determined the quantity taken up the animal when exposed to the dust-laden air. He observed that only 4 to 24 per cent. of dust entering the

nose was deposited in the respiratory organs, while the remaining quantity found its way to the intestine.

More recently Boer has made a relative quantitative estimation of the soot content of small portions of lung tissue. By his method, using only 3 ccm. of lung tissue, errors of calculation may possibly be great. He points out the error which would be obtained in comparing lung tissue of unequal density or consistence, as for example that of emphysema or oedma, and confined his examination to normal lung tissue. Here, too, much variation may be encountered, whether or not much pigmented pleura is included in the portion under examination. Care in selection of the tissue can not wholly rule out errors of serious import in the results. Furthermore, as the amount of carbon in these small portions of tissue was too small to weigh, he has used a colorimetric method suggested by Liefmann. The amount of carbon isolated from the lung examples was suspended in a mixture of oil and ether, and compared with a set of standard suspensions, prepared by suspending weighed quantities of naphthalin soot in the same vehicle. Such a colorimetric method cannot be relied upon, owing to the difference in the nature of the carbon in the lungs and naphthalin soot. Fresh soot has physical and chemical properties widely different from the carbon isolated from the lung by treatment with antiformin and alcohol. Isolated carbon from lungs has lost its flakiness and is quite granular, devoid of its phenols and acids. Its bulk is much less than the original soot from which it was derived, and in suspensions taken, weight for weight, it does not compare with the apparent mass of soot. It is furthermore, to be noted that in isolating the lung carbon, care must be taken to free the final product of its fat and foreign calcareous matter which tends to remain incorporated in the residue.

In our determinations we took an entire lung, dissected away the glands, large bronchi and adventitious tissue at the hilus, and minced the entire organ in a meat machine. The pulp was then divided among four half-liter flasks and to each was added enough of a seventy-

five per cent. solution of antiformin to well fill the flask. The flasks were placed in the incubator and repeatedly shaken for four to six days. Two hundred cubic centimeters of alcohol were then added to each flask and the mixture centrifugalized, the residue being collected and returned to clean flasks. These materials were again subject to fresh digestion with antiformin for a period of four days, recollected, washed and for a third time acted upon by antiformin. After again collecting the residue and washing it, it was treated with ten per cent. hydrochloric acid, repeatedly agitated and allowed to remain in contact for forty-eight hours. The residue now collected by the centrifuge and washed, was in turn treated with acid-alcohol and ether until the supernatent fluid showed no evidence of fat. The ether suspension was then allowed to evaporate to dryness, and the collected residue repeatedly washed with distilled water to rid it of any contained salts. The final product consisted of a pure black, fine powder, denser than the light, fluffy soot masses found in the air. Under the microscopic, angular carbon particles were alone present.

Case	Age	Occupation	Residence	Side	Quantity of Carbon
218	22	Laborer	Pittsburgh	Right	3.2
73	28	Peddler	"	Left	5.3
154	37	Laborer	"(6 yrs.)	Right	1.7
163	37	Housekeeper	"	Right	2.1
158	39	Clerk	"	Left	1.2
164	44	Housekeeper	"	Right	2.6
A-Q-8	47	Storekeeper	Ann Arbor	Right	0.145
A-Q-12	68	Laborer	"	Right	0.405
239	69	Carpenter	Pittsburgh	Right	2.81

(NOTE.—I am indebted to Prof. A. S. Warthin for the material from Ann Arbor.)

In our examination it is shown that the lungs of adult individuals resident in the Pittsburgh district have materially more carbon deposit than the lungs of the two individuals resident in a lesser manufacturing community.

Our number for comparison is very small, but is, nevertheless, suggestive of community characteristics. On account of the slow and rather tedious process in isolating the carbon in a pure form, only one lung was examined in each case, so that the total pulmonary content is about double of that indicated in the table. Furthermore, it is to be noted that the isolation of the carbon did not include that present in the peri-bronchial glands, where dense deposits are commonly found.

As was previously indicated the lungs showing marked anthracosis are decidedly heavier than normal organs, but it must not be inferred that the extra weight is due to the foreign dust in the lungs. From our analysis of the carbon pigment in the lung it is evident that no material increase in weight is obtained directly from this source. On the other hand, it is well shown that a relatively small quantity of carbon in the lung can induce massive fibroid changes which alter the architecture and increase the bulk.

SUMMARY.

Pulmonary anthracosis (not in coal miners) is distinctly an urban disease, and is proportionate to the smoke content of the air.

The soot is inspired and lodges in the pulmonary alveoli, from which it is carried by phagocytes into the lung tissue to become lodged in some portion of the pulmonary lymphatic system.

Although small quantities of carbon deposit in the lung may remain without harm, yet the quantity accumulating in the dweller of the larger cities has an accompanying greater or less fibrosis impairing the elasticity as well as altering the functional capacity of the organ.

The distribution of carbon is fairly uniform in the parenchyma of the different lobes, but there is a considerable variation in the distribution of the pleural deposit. The interlobar and diaphragmatic pleural surfaces show the least pigment. Moreover, less pigment is found in the grooves produced by the ribs or abnormal bands.

Carbon tends to accumulate at the nodal points of junction of the lymphatic channels. The cellular migration of carbon may lead to unusual accumulations in certain areas particularly well demonstrated in the deposit about chronic tuberculous lesions.

Carbon deposits by inducing fibrosis tend to encapsulate chronic tuberculous foci.

Pulmonary anthracosis by itself does not appear to stimulate the production of pleural adhesions.

The actual amount of carbon present in the lungs of different individuals varies considerably and is dependent, in part at least, to the age, occupation, residence and condition of the lungs (emphysema, collapse, tuberculosis).

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The Bacteriology of Soot*

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The study of soot from a bacteriological standpoint has received but scant attention from the numerous investigators of the problems of the smoke nuisance.

Needless to say the subject has not been left out of the discussions; in fact, it is rather frequently mentioned in a more or less general way. As far as I have been able to ascertain, however, there has been but little definite work on the Bacteriology of Soot as discussed in this paper.

In an article in the *Revue Industrielle* (1), is found the question, "Are we going to learn one of these days that smoke, thanks to its antiseptic properties, contributes to making the atmosphere healthy?" Glinzer (2) refers to the fact that the particles contained in soot possess excellent germicidal and disinfecting qualities. Racine (3) in a discussion on the "Relation of Emphysema and Tuberculosis to coal-lungs in miners," believes from his own observations that anthracosis of the lungs acts as a protective influence against tuberculosis and that the only correct view is that coal has a great disinfecting power and that the conserving action of the coal dust is, perhaps, to be explained "from its action as a hinderance to the growth of microorganisms such as the bacilli of tuberculosis." We were unable to find in the literature any original work upon which these conclusions could be founded. Percy Frankland (4) shows that fogs do not tend to con-

centrate or nurture bacteria, for he found there were remarkably few bacteria in London air during a fog. On the other side of the question, Russel (5) includes the increased number of bacteria in a list of contributory causes of the high death rates during fogs. Sir William Ramsay (6) first brought forward the theory that smoke by directly absorbing light, through the action of clouds and fogs, which are particularly fitted to absorb the blue, the violet and ultra-violet rays, which are the germicidal rays in light, contributes to the development and increase of bacteria, pathogenic as well as others, in the atmosphere. Liefmann (7) also believes that under the above conditions "bacteria, especially the pathogenic ones, are permitted to thrive." In passing it may be mentioned that there is no evidence that bacteria ever grow in the air. They are carried into it from a variety of sources, are continually falling out of it by gravitation, being carried out by rains, or destroyed in a number of ways. The effect of the gases in the air upon bacteria is another problem, although it is closely related to the one under discussion. The contamination of the air of our cities with sulphur dioxide is well known (8); also that surphur dioxide in the air acts as a disinfectant, the necessary proportion being not less than 92 grams of sulphur per cubic meter (9). Cohen and Ruston in "Smoke—A study of town air," have devoted some space to the consideration of the effects of acid rains upon the bacteria of the soil. They point out that the greatest reduction takes place in the numbers and the activity of the nitrifying or nitrate producing bacteria, there being also a marked inhibitory effect on the nitrogen fixing organisms.

In our investigations we examined the air of Pittsburgh to determine the numbers and distribution of bacteria in different parts of the city and to ascertain, if possible, if any relation exist between the bacterial count and the smoke conditions.

For this purpose twenty glass evaporating dishes seven inches in diameter filled with agar-agar were ex-
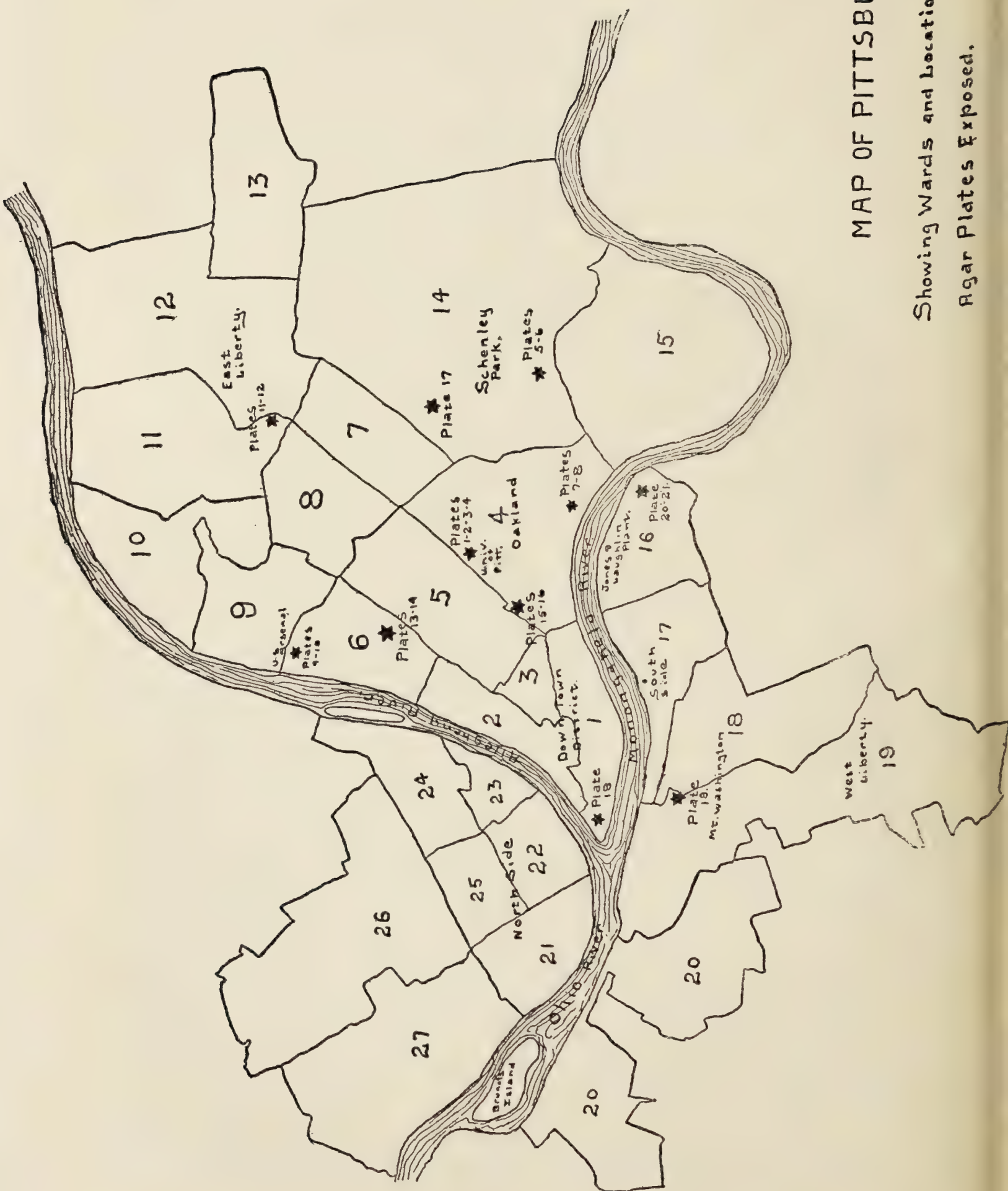
MAP OF PITTSBURGH.

Showing Wards and Location of

Agar Plates Exposed.

posed for from five to fifteen minutes in various districts. Notes were taken of the presence or absence of smoke, the wind direction, the condition of the earth, whether moist or dry, and time of exposure. The number of colonies developing in forty-eight hours at 37° C. varied within very wide limits and it was found impossible to discover any influence of the smoke content of the air on the bacterial count. The difficulty of attempting to draw any definite conclusions from these experiments will be patent to everyone, the factors which influence the bacterial content of the air being so numerous and so variable as—rain, moist or dry soil, winds, sunlight, and other conditions. The map of the city shows the points where plates were exposed and Table I gives our findings in a condensed form.

One quite striking observation, however, was made and that was the comparative infrequency of the development of colonies around the soot particles. Rough microscopic counts were made of the total number of visible soot particles and of those which were infected, as indicated by a black speck in the center of the colony. Out of about 500 counted, 100 showed growth. Many of these particles which we counted as soot, were, in all probability, specks of dust from other sources, so that our proportion of infected soot particles is too high. In several of the plates the soot particles were too numerous to count and around the majority of these no growth was to be noted. This was particularly true in the case of Plates 9 and 10, where the atmosphere was decidedly smoky. Considering the sources from which bacteria enter the air this is not to be wondered at. The smoke as it leaves the chimney is free from bacteria and apparently is not a favorable nidus for their collection from the air into which it is poured.

The common types of aerobic Gram positive spore-bearing bacteria and chromogenic organisms were isolated on our plates. B. Coli Communis and Communior, B. Alkaligenes Fecalis, B. Proteus Vulgaris, B. Pyocyaneus,

Plate Number See Map.	Time of Exposure in Minutes.	Weather.	Wind.	Smoke.	Count.	Notes.
1	15	Cloudy, rain 3 hrs. before.	N. W.	None	75	B. Coli Communis isolated.
2	15	Cloudy, rain 3 hrs. before.	N. W.	"	53	
3	5	Cool, cloudy; soil damp.	W.	"	15	
4	10	Cool, cloudy; soil damp.	W.	"	68	
5	15	Clear, warm; soil damp.	W.	B l o wing to-wards plates but high.	26	B. Coli Communis. B. Coli Communior.
6	10	Bright sunshine; soil damp.	W.		43	B. Aikaligenes. Fecalis.
7	10	Cloudy, sultry; soil dry.	S.	B l o wing to-wards plates.	51	5 soot particles, no growth.
8	15	Cloudy, sultry; soil dry.	S.		144	15 soot particles, 3 infected.
9	10	Partly cloudy.	S.	Smoky.	60	Soot particles very numerous, 1 in-fected.
10	15	Warm, dry.	S.	"	108	Soot particles very numerous, 3 in-fected.
11	5	Clear, warm, sultry; soil dry.	S.	Hanging low.	18	Several soot parti-cles, no growth.
12	15	Clear, warm, sultry; soil dry.	S.	Same.	46	Few soot particles; 1 i n f e c t e d. B. Proteus Vulgaris.
13	10	Bright, hot, dry, sultry.	S.	Valley smoke not dense near plates.	59	No soot particles. Nocardia.
14	15	Threatening rain.	S.		—	Fly c o n t a minated plate.
15	5	Threatening rain; rain 1 hr. before.	E.	B l o wing to-wards plates.	116	B. Pyocyaneus. Soot particles 130; 14 infected.
16	8	Threatening rain; rain began.	E.	Same.	124	Soot particles 174; 17 infected.
17	10	Threatening rain; 2 hrs. before.	E.	Air smoky.	19	No soot particles.
18	10	Hot, clear, dry, dusty.	S. W.	Dirty, dusty, smoky.	196	Soot particles 11; 4 infected.
19	10	Hot, clear, dry, dusty.	S. W.	Valley smoky, clear near plates.	160	Soot particles 19; 11 infected; air no-cardia.
20	5	Hot, clear, dry, dusty.	S. W.	B l o wing to-wards plates.	131	Soot particles 72; 30 infected.
21	10	Hot, clear, dry, dusty.	S. W.	B l o wing to-wards plates.	128	Soot particles 56; 14 infected.

and others, presumably from manure dust, and a few examples of air nocardia were also found.

Our next problem was to determine the action of soot on the growth of bacteria. For this purpose a quantity of soot was obtained from the special chimney in the Department of Industrial Research.

The partial analysis was as follows:

Tar,	3.84%
Ash	1.19%
Fixed Carbon	94.97%

This specimen was used throughout the experiments.

The analyses of specimens of soot collected from the air in different parts of the city showed some wide variations.

Woods Run.

Tar	0.82%
Ash	62.6%
Fixed Carbon	36.58%

State Hall.

Tar	0.36%
Ash	66.68%
Fixed Carbon	32.96%

This soot, even after standing around the laboratory in an ordinary cardboard box frequently open to the air, was shown by experiment to be almost free from bacteria. Five agar plates dusted with small quantities of this unsterilized soot failed to show growth with the exception of one colony on one plate. The soot was now added in varying amounts to test tubes of ordinary broth. No growth occurred. However, when larger quantities of this same soot were added to 150 cc. of broth in flasks, growth of bacteria did appear. The organisms developing being of the B. Subtilis group.

Experiments were next undertaken to determine the bactericidal action, suggested by the above observations.

Efforts were made to determine any difference in growth
in flasks of broth containing soot from other control
flasks without soot.   Dilution and plating methods were
employed but the mechanical interference of the soot par-
ticles in the one case ruled out the method as one with-
out even approximate exactness.   The counts, however,
were uniformly lower in the soot broth than in the control.
A series of agar plates, one having the surface sifted with
soot, the other free, were next exposed in the laboratory
and counts made of the colonies from the aerial con-
tamination.   No marked difference in the number of colo-
nies was found.

The following series of experiments have, however,
given us quite definite results indicating a very marked
bactericidal action of soot.   Five grams of soot were thor-
oughly mixed with 100 cc. of broth 0.6 acid to phenolp-
thalein.   After autoclaving, the mixture was allowed to
stand several days.   The soot particles were then filtered
out and the filtrate after sterilization was seeded with B.
Typhosus.   A control flask was inoculated at the same
time.   No growth occurred in the soot-treated broth while
a good growth developed in the control.

A second experiment was carried out.   The broth
after treatment with soot as before was tubed and inocu-
lated with a series of organisms.   Controls of plain broth
from the same batch were used for comparison.   Fresh
twenty-four hour cultures were employed.   The results are
seen in Table II.

The soot broth tubes which showed no growth after
seeding and incubation, did not show any growth on fur-
ther transfers with the exception of B. Subtilis.   The
spores in this case had most probably withstood the action
of the bactericidal substance.   B. Coli Communior and
B. Indicus showed much less growth in the soot-treated
broth than in the control.   B. Pyocyaneus was apparently
unaffected while B. Paratyphosus (Achard) and B. Pro-
teus Vulgaris showed definite agglutination in the soot-
treated broth.

TABLE II.

Culture.	Soot Broth.	Control.
Staph. Albus	—	+ + +
Staph. Pyog. Aureus	—	+ + +
B. Coli Communis	+ +	+ + +
B. Coli Communior	+ +	+ + +
B. Mucosus Capsulatus	+	+ + +
B. Acidi Lactici	—	+ + +
B. Typhosus (3)	—	+ + +
B. Typhosus (90)	+	+ + +
B. Paratyphosus B.	—	+ + +
B. Paratyphosus Achard	+ +	+ + +
B. Dysenteriæ (Flexner)	—	+ + +
B. Pseudodysenteriæ	—	+ + +
B. Iliacus	—	+ + +
B. Proteus Vulgaris	+ + +	+ + +
B. Alkaligenes Fecalis	—	+ + +
V. Cholera	—	+ + +
B. Pyocyaneus	+ + +	+ + +
B. Indicus	+	+ + +
B. Subtilis	—	+ + +
B. Mesentericus	—	+ + +
B. Xerosis	—	+ + +
B. Diphtheriæ (230)	—	+ + +

(The intensity of the growth is indicated by the number of + signs.)

We believed that this inhibitory and bactericidal action was due to the phenols contained in the soot. The soot-treated broth gave a marked reaction for phenols by Millon's reagent while the control broth gave a negative reaction. After testing the acidity, phenolphthalein being used as the indicator, it was found that the soot treated broth gave a difference of 1.7 per cent. acid over the untreated broth, the acidity of which was 0.6 per cent. To determine whether this acidity was the potent inhibitory factor we carried out the following tests.

A new lot of broth was prepared and the reaction made 0.6 per cent. acid. To 500 cc. of this broth 25 grams of soot were added. The mixture was thoroughly shaken, autoclaved and allowed to stand for two days, with repeated shaking and finally filtered. The reaction titrated against N/20 sodium hydrate expressed in terms of hydrochloric acid was found to be 2.2 per cent. acid. One-

half of the broth was used at this acidity, 2.2 per cent. the other half being reduced to 0.6 per cent. by addition of sodium hydrate. Half of the untreated control broth had its acidity raised to 2.2 per cent. acid with hydrochloric acid. The four lots were then tubed, sterilized and inoculated with a number of organisms from twenty-four hour agar slants. After an incubation of seventy-two hours, the results obtained were as shown in Table III.

From this it will be seen that we must consider at least two factors in the antiseptic action of the soluble content of soot in broth. The effect of the increased acidity which is seen most markedly in the cultures of the cholera vibrio where practically no growth took place in either of the acid broths is of great importance. The cholera organism is shown to be particularly sensitive to the presence of acid and for its cultivation an alkaline or neutral medium must be employed. Schroeder (10) has shown that the Vibrio choleræ is killed after an exposure of five hours to peat dust. It is especially effective, he says, if the peat be of an acid reaction.

The growth of B. Anthracis and B. Subtilis is also inhibited in the broths of high acidity, while B. Alkaligenes Fecalis and B. Iliacus, are definitely affected. It is interesting to note the effect of the acidity in interfering with the production of the coloring matter in the cultures of B. Pyocyaneus. Russel, Cohen and Ruston, and others point out the variable acid content of soot. On the other hand we notice, that, independently of the acidity, the soot-treated broth exercises a marked interference with growth. This is to be seen with B. Indicus, one strain of B. Coli Communis, B. Typhosus, and in B. Paratyphosus to a marked degree. The two latter organisms are not generally affected by small amounts of acid, and are, therefore, valuable in testing out this second bactericidal effect of the soluble parts of the soot.

Soot probably has the power of absorbing many gases from the air especially those associated with the combustion of coal.

The next problem was to study the effect, if any, of soot on the destruction of bacteria in the process of dessication.

TABLE III.

Culture.	Control Broth. 2.2 Acid.	Soot Broth. 2.2 Acid.	Control Broth. 0.6 Acid.	Soot Broth. 0.6 Acid.
B. Indicus	Heavy cloud.	Trace of cloud.	Heavy cloud, heavy precipitate.	Slight cloud.
B. Pyocyaneus..	Heavy cloud, powdery scum, trace of green color.	Same, no green color.	Same, bright green on top.	Heavy cloud, thick compact scum, green color throughout.
B. Anthracis......	Clear, no precipitate.	Clear, no precipitate.	Clear, abundant precipitate.	Clear, slight precipitate.
B. Subtilis	No growth.	No growth.	Heavy ring, heavy precipitate, granular cloud.	Ring on glass, precipitate.
B. Coli Communis (52) and (14).........	Marked cloud.	Slight cloud.	Marked cloud.	Slight cloud.
B. Coli Communis from urine (780) ..	Fair cloud.	Same.	Same.	Same.
B. Typhosus	Cloud.	Slight cloud.	Heaviest cloud.	Faint cloud.
B. Paratyphosus B.	Marked cloud.	Faint cloud.	Marked cloud.	Faint cloud.
B. Proteus Vulgaris	Heavy cloud, no scum.	Heavy cloud, scum.	Very heavy cloud, no scum.	Very heavy cloud, scum.
B. Iliacus..........	Slight cloud.	Fair cloud.	Heaviest cloud.	Heavy cloud and ring.
B. Alkaligenes Fecalis	Faint cloud.	Clear.	Marked cloud, scum.	Slight cloud.
V. Cholera.........	Clear.	Trace of cloud.	Cloud.	Cloud.

Dessication is one of the most valuable natural means of disinfection and many organisms succumb to its effects very rapidly as the gonococcus, the B. Influenza, the meningococcus and others. The micro-organisms of the air, on our streets, and in our houses are continually being destroyed by this process and we have been able, we believe, to show that soot increases very decidedly, this bactericidal action.

TABLE IV.

Exposure.	Influence of Soot on B. Indicus.		
	Control. Cover Glass. Dipped in Broth and Dried.	Cover Glass I. Dipped in Soot while Moist, then Dried.	Cover Glass II. dried as in Control. Buried in Soot.
1 day............ ...	+	+	+
2 "	+	+	+
3 " ....·.......	+	+	+
4 "	+	—	+
5 "	+	—	+
7 "	+	—	—
8 "	+	—	+

(The + sign indicates that growth was obtained in the test cultures.)

TABLE V.

Exposure.	Culture.	Influence of Soot on B. Typhosus and Streptococcus Fecalis.		
		Control Dipped in Broth and Dried.	Cover Glass I. Dipped in Soot while Moist, then Dried.	Cover Glass II. Dried as in Control. Buried in Soot
2 days..........	B. Typhosus	+	—	
	S. Fecalis	+	+	
3 "	B. Typhosus	+	—	+
	S. Fecalis	—	—	—
	B. Typhosus	+	—	+
	S. Fecalis	+	—	+
4 "	B. Typhosus	+	—	+
	S. Fecalis	—	—·	+
5 "	B. Typhosus	+	—	+
	S. Fecalis	+	-·-	—
6 "	B. Typhosus	+	—	+
	S. Fecalis	—	—	—
9 "	B. Typhosus	+	—	+
	S. Fecalis	—	—	—
10 "	B. Typhosus	+	—	—
	S. Fecalis	+	—	—

The technique of our experiments was as follows: Fresh twenty-four hour broth cultures of the organisms to be tested were prepared. Small sterile cover glasses were thoroughly moistened by dipping them into the cultures. These were dried under sterile precautions for sixteen to twenty-four hours over caustic soda. They were then transferred to sterile petri dishes and used as controls.

Cover glasses indicated under the heading I in the table, were dipped into the broth cultures and then into sterile soot and finally dried as in the control. Cover glasses under heading II in the table were prepared in the same way and at the same time as the control, and when dry were packed in sterile soot. From time to time these cover glasses were dropped into tubes of dextrose broth to test the viability of the organisms.

It will be noted that the failure of growth is shown very clearly in the case where the moist cover glass was dipped in soot and then dried. In the majority of cases those cover glasses which were first dried and then packed in soot failed to show growth much later than the above, but usually before the control. This is well shown in Table V.

The long period that the Streptococcus Fecalis, 174 days, and Staphylococcus Pyogenes Aureus, 225 days, remained viable under these abnormal conditions is quite remarkable. (See Table VI.)

In Table VII is shown the peculiar behavior of yeast. It survived longest, 41 days, on the cover glasses dipped in soot while still moist, the conditions under which all the other organisms tested rapidly died out. Marshall (11) quotes Hansen as stating that compressed beer yeast mixed and dried with charcoal kept as long as ten years. The marked resistance of the yeast organism to the action of acids is also of importance in this connection.

The great natural disinfectant of the atmosphere and our surroundings is the bactericidal action of the sun's rays. Direct sunlight is most destructive and its activity

TABLE VI.

Time of Exposure	Incubation Period	Culture	Control. Dipped in Broth and Dried	Cover Glass I. Dipped in Soot while Moist, then Dried	Cover Glass II. Dried as in Control. Buried in Soot
		Influence of Soot on B. Coli, B. Typhi, Streptococcus Fecalis and Staphylococcus Aureus.			
2 days	24 hours	B. Coli	+	+	
		B. Typhosus	+	+	
		Strep. Fecalis	+	+	
		Staph. Pyog. Aureus	+	+	
5 "	24 "	B. Coli	+	—	+
		B. Typhosus	+	+	+
		Strep. Fecalis	+	—	+
		Staph. Pyog. Aureus	+	—	+
	48 "	B. Coli	+	+	+
		B. Typhosus	+	+	+
		Strep. Fecalis	+	—	+
		Staph. Pyog. Aureus	+	—	+
6 "	24 "	Strep. Fecalis	+	+	+
		Staph. Pyog. Aureus	+	—	+
7 "	24 "	B. Typhosus	+	—	+
		Strep. Fecalis	+	+	+
19 "	24 "	B. Coli.	+	—	+
		B. Typhosus	+	—	—
		Strep. Fecalis	+	—	+
		Staph. Pyog. Aureus	+	—	+
	48 "	B. Coli	+	—	+
		B. Typhosus	+	—	—
		Strep. Fecalis	+	+	+
		Staph. Pyog. Aureus	+	—	+
34 "	24 "	B. Coli	+	—	—
		B. Typhosus	+	—	—
		Strep. Fecalis	+	—	+
		Staph. Pyog. Aureus	+	—	+
	48 "	B. Coli	+	—	—
		B. Typhosus	+	—	+
		Strep. Fecalis	+	—	+
		Staph. Pyog. Aureus	+	—	+

TABLE VI (*Continued*).

Time of Exposure	Incubation Period	Influence of Soot on B. Coli, B. Typhi, Streptococcus Fecalis and Staphylococcus Aureus.			
		Culture	Control. Dipped in Broth and Dried	Cover Glass I. Dipped in Soot while Moist, then Dried	Cover Glass II. Dried as in Control. Buried in Soot
62 "	24 "	B. Coli	+	—	—
		B. Typhosus	—	—.	--
		Strep. Fecalis	—	—	—
		Staph. Pyog. Aureus	—	—	—
	48 "	B. Coli	+	—	—
		B. Typhosus	—	—	—
		Strep. Fecalis	+	—	+
		Staph. Pyog. Aureus	+	—	+
174 "	24 "	Strep. Fecalis		—	+
		Staph. Pyog. Aureus	—	—	+
225 "	24 "	Staph. Pyog. Aureus	+	—	—
247 "	24 "	Staph. Pyog. Aureus	—	—	—

upon bacterial life depends directly on the amount of moisture and dust in the air.

Smoke, in contributing very great numbers of minute particles to the air adds to the conditions favoring fogs and clouds. Smoke, fogs, and clouds, all absorb more or less, the blue, the violet, and ultra-violet rays of the sunlight. This is well seen in the familiar red sun of a smoky atmosphere. These particular rays, which are absorbed, give the important bactericidal action to the sunlight. Most of the above facts have been amply proved by other experiments and it was not considered advisable to repeat them. We have, however, made a few observations on the protective action of soot for bacteria.

The technique of our experiments was briefly as follows: Agar-agar, well seeded with the test organism, was poured into petri dishes. Soot was sifted over one half

of the cover of the petri dish while the other half remained free. These plates were then exposed to the sunlight for definite periods, then incubated and the results read.

A number of plates, seeded with Staphylococcus Aureus, were exposed to sunlight for varying periods every day for two weeks. The results obtained are shown in Table IX. Notwithstanding the irregularity of these results the protection, afforded by the soot in the air and clouds against the action of the sun's rays, is, I believe, clearly shown.

There are a number of very interesting questions which arise as a result of these experiments. It has been shown that soot in contact with bacteria has very decided bactericidal properties. These properties are also demonstrated in the soluble content of the soot. The soot particles from the air as they fell on our plates were generally sterile. This may be due to the solution of the bactericidal substances of the soot by the moisture on our plates, with the consequent destruction of any bacteria adherent to the soot. Or the moisture condensing around the soot as it does in the formation of fogs and clouds, may have acted in the same way before it was collected on our plates. The third possibility is that the majority of the soot particles never came in contact with bacteria after leaving the chimney, at which time they were, of course, bacteria free.

That this disinfectant substance requires moisture in order to have its most powerful effect is well shown in the drying experiments where the organisms treated with soot, while still moist, succumbed very much sooner than the others. There is also the possibility that the soot absorbs moisture from the bacteria and hastens thereby its death by thorough drying. This was suggested in the experiment in which dried organisms were buried in soot and frequently killed off earlier than in the control.

TABLE VII.

Time of Exposure	Incubation Period	Influence of Soot on B. Diphtheriæ and Yeast (Saccharomyces).			
		Culture	Control. Dipped in Broth. then Dried	Cover Glass I. Dipped in Soot while Moist. Dried	Cover Glass II. Dried as in Control. Buried in Soot
3 days	48 hours	B. Diphtheriæ	+	—	
		Yeast	+	+	
	72 "	B. Diphtheriæ	+	+	
		Yeast	+	+	
7 "	24 "	B. Diphtheriæ	+	—	+
		Yeast	—	—	—
	48 "	B. Diphtheriæ	+	—.	+
		Yeast	+	+	+
	72 "	B. Diphtheriæ	+	+	+
		Yeast	+	+	+
16 "	48 "	B. Diphtheriæ	+	—	+
		Yeast	—	+	+
	72 "	B. Diphtheriæ	+	+	+
		Yeast	—	+	+
27 "	72 "	B. Diphtheriæ	+	—	÷
		Yeast	—	+	—
38 "	48 "	B. Diphtheriæ	+	—	+
	5 days	B. Diphtheriæ	+	+	+
41 "	48 hours	B. Diphtheriæ	+	—	+
		Yeast	—	+	—
77 "	72 "	B. Diphtheriæ	—	—	—
		Yeast	—	—	—

That the conditions, similar to those of our experiments, are to be found in every smoky city, will be evident to any one who has noticed the black, smeary deposit of soot on damp days where the concentration of soluble substances from the soot in crevices and corners must be very high. We have found, as others have demonstrated, that the effect of soot in fogs and clouds in diminishing the action of the run's rays on bacteria, is quite definite. The relative importance of the protective qualities of soot against sunlight to the bactericidal effect of the constituents of soot remains an open question.

There are, therefore, two divergent results brought about by the presence of soot in our atmosphere and upon the earth's surface. One of these is beneficial and the other harmful to the life of vegetable micro-organisms, and from the bacteriological and hygienic point of view may serve as a direct aid in propagating or preventing the spread of infectious disease.

TABLE VIII.

Organism Tested.	Inhibition of Solar Bactericidal Activity.			
	Time of Exposure	Incuba- tion	Soot Covered Half.	Unprotected Half.
Strep. Fecalis.............	5 mins.	24 hrs.	Few colonies	None
	5 "	48 "	Many "	Many colonies
	15 "	48 "	Few "	No growth
	30 "	48 "	Few "	Many colonies
	45 "	48 "	Few "	Many "
	45 "	48 "	Many "	Few "
	120 "	48 "	Many "	Few "
B. Indicus..................	10 "	48 "	Many "	Many "
Staph. Aureus.............	10 "	48 "	Many "	Many "
	30 "	48 "	Many "	Many "
	45 "	48 "	Many "	Few "
	75 "	48 "	No "	No "
B. Mesentericus...........	15 "	48 "	Few "	Few "
	30 "	48 "	Few "	Few "
	45 "	48 "	Few "	Few "
	60 "	48 "	Few "	Few "
	75 "	48 "	Few "	Few "
	180 "	48 "	Few "	Few "

GENERAL CONCLUSIONS.

1. Soot has a definite bactericidal action on bacteria, due either to the absorption of moisture from the organisms or more probably, to the action of its contained germicidal acids and phenols.

2. Soot as it exists in the air does not form a favorable nidus for the collection and distribution of bacteria.

3. Broth and other fluids treated with soot have conferred upon them a decided germicidal power.

TABLE IX.

(Inhibition of Solar Bactericidal Activity by Smoke. Test Organism Staphylococcus Pyogenes Aureus.)

	Sun.	Clouds.	Smoke.	Result.	Note.
1	Bright		Clouds low.	Killed 1 hr.	
2	Dull	Present.	Clouds passing over sun.	Slight difference in 1 hr.	
3	Bright	Passing across sun.	None.	Killed 1 hr.	24 hr. incub.
4	Bright	Same.	"	Lessened in 15 and 30 mins. in proportion.	
5	Hidden, dull	Snowing in morning. Present.	"	Killed in 1½ hrs.	
6	Bright	Thin and white.	Around horizon.	Not killed in 1 hr., lessened.	
7	Clear	—	Haze around horizon.	Same.	
8	Bright and clear	Very few.	—	35 mins., much lessened; 1 hr., almost all killed.	
9	Bright and variable ..	Cloudy.	—	Not killed in 1 hr.	
10	Bright	None.	Much, low down.	Not killed in 1 hr.	Around edge.
11	Dull, foggy	Foggy.	—	Little change in 1½ hrs.	
12	Dull	Many, raining.	Much.	Almost all killed in 1½ hrs.	
13	Variable, free, dull	Variable.	—	Little change 1¾ hrs.	
14	Bright	None.	Haze.	Killed in 1 hr.	

4. This germicidal action is due not only to the acids contained in the soot but also to some other agent, probably some of the phenols.

5. Soot, as it occurs in smoke, clouds, fogs, and as a non-transparent covering for our streets and houses, protect micro-organisms from the destructive action of the sunlight.

I wish to express my thanks to Mr. C. H. Marcy for his valuable assistance in the early part of the work, more

especially in the study of the bacteriology of the air of Pittsburgh. I wish also to thank Dr. O. Klotz for many suggestions and Mr. Benner for the samples of soot and the chemical analysis of the same.

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Some Histological Evidences of the Disease Importance of Pulmonary Anthracosis*

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The histological evidences as to the disease importance of anthracosis of the lungs, as set forth in this paper, are the results of work done by the author in an attempt to determine whether or not extensive deposits of dust and coal pigment within the body tissues have or have not any "real disease" significance. The problem as originally planned included a study of all of the microscopic effects of smoke and soot upon the body as a whole. Such a piece of work has been impossible in the time at our disposal so that in the present paper we shall deal only with the microscopic effects of smoke and soot, as observed upon the air passages and lungs, which are the chief portals of entry for these substances into the body. We have also included a consideration of the association of the resultant pulmonary lesions with those of tuberculosis and pneumonia.

The paper naturally divides itself into three parts, and for the sake of clearness these will be discussed under the headings of: I. The anthracotic process; II. The association of anthracosis and tuberculosis; and III. The association of anthracosis and pneumonia.

In the use of the term anthracosis in this report it must be understood that it refers only to the fairly well

advanced stages of the process, as will subsequently be described.

The tissues studied were obtained in part from the surgical and autopsy materials of the Department of Pathology of the University of Pittsburgh, and from the Mercy Hospital, and in part from experimentally produced lesions in animals.

I. The anthracotic process.—Anthracosis is a term applied to a condition in which carbon particles of extraneous origin are deposited in the tissues or organs. It has been described as occurring in the lungs, spleen, liver, intestinal tract, and certain sets of lymph nodes, and is always accompanied by more or less fibrosis on the part of the tissues in which it is found. The most common site for anthracosis is in the lungs, and in individuals who work or live in smoky, sooty atmospheres; it often reaches a marked degree of development.

The fine particles seem to gain entrance into the lung substance by way of the air passages, and it has been stated by some that the mucous membranes of the nose, mouth, pharynx, larynx, trachea, bronchi, and bronchioles contribute largely to the taking in of the pigment, but our observations tend to show that in this community (Pittsburgh), at least, such is not the case. In the nasal cavities, the vibrissæ, and turbinates collect a great deal of carbon, which is subsequently removed by the secretions, for in the examination of nasal polypi and strips of turbinate mucosa removed at operations we have never seen a single example of free pigment or pigment bearing cells beneath the epithelial layer. Maclachlan[1] in his paper on "Tonsilitis" in which he reported a histological study of three hundred and fifty pairs of tonsils found only one example of a carbon pigment bearing cell in that structure, and about as many more tonsils and adenoids have since been examined without finding another instance. In the air passages below the larynx, pigment bearing cells have frequently been observed, but these were either free in the lumina or were surrounded by bits of mucus and other

cells and were not found penetrating the epithelial layers. In abscesses of bronchi, both the abscess contents and remaining parts of the mucosa have been seen to contain pigment bearing cells, though one could not say that any of these were definitely passing into the tissues. Moreover, our contention is supported by the following two experiments:

Experiment I.—For twenty minutes daily a young guinea-pig was placed in a box through which a dense black smoke was made to pass. The smoke was generated by burning xylol and entered the box through a funnel. After each exposure the animal showed a profuse nasal secretion and sneezed repeatedly. His furry coat was completely blackened. At the end of ten days he was killed with chloroform and autopsied. Macroscopic description: The gross findings of soot deposit were entirely limited to the blackened nasal mucosa, which was especially marked over the anteriar portions of the turbinates. Microscopic description: Sections showed soot particles adherent over the epithelium of the nasal mucosa. There was no evidence of pigment phagocytosis. (**Note.**—Nothwithstanding the fact that three guinea-pigs with early spontaneous anthracosis have come under our notice we failed in our attempts to reproduce the condition experimentally, apparently on account of the efficient way in which the intricately arranged turbinates protected the air passages beyond them.)

Experiment II. A white rabbit was given sixty inhalations in eighty-seven days of finely powdered lamp black in the following way: The nose piece of a powder insufflator was placed in the animal's mouth and the lamp black was forced in under pressure. At first the inhalations were given every two or three days, but later the treatment was carried out daily. The animal became very much emaciated and died. The autopsy was performed while the tissues were still warm. Macroscopic description: All of the mucous membranes of the mouth, pharynx, esophagus, stomach, larynx, trachea, and bronchi were coated or crusted with black pigment. Many of the lesser bronchi were completely plugged with masses of lamp black so that the foci of lung beyond them were devoid of air and in a stage of collapse. A few fine black granules were seen in the lung tissue. Microscopic description: In no part of the upper air passages was the phagocytosis of pigment observed. No pigment was seen in or beneath the epithelial layers of the bronchi, though some of them contained sufficiently large masses of pigment in their lumina to cause a flattening of the epithelial lining cells. In the alveoli many pigment phagocytes were seen (Fig. 5), and these cells were especially numerous in the atelectatic areas; some of them had already penetrated into the spaces of the alveolar walls, but as yet none had reached the perivascular, peribronchial, or subpleural lymphatics. The peribronchial lymphoid tissue was also free from pigment. The carbon pigment cells were large and round and were so completely filled with granules that their identity was obscured.

It will be seen by these two experiments that although we were able to bring an abundance of carbon pig-

ment in direct contact with the epithelial linings of the oral cavity and upper air passages we were unable to obtain any evidences of phagocytosis of such pigment in any of these structures. Coupling these results with our negatice findings in the surgical and autopsy materials cited above, we feel justified in concluding that the amount of pigment phagocytosis in the air passages above the lung alveoli must be a negligible quantity.

As our studies on the anthracotic process have to do largely with the lung alveolus and with the lymphatics of the lung a hasty review of our knowledge of these structures seems advisable at this point.

The alveoli, or air sacs, are minute cuboidal or spheroidal cavities which open directly into the small bronchioles through the infundibuli. The cavities are lined by a single layer of very flat pavement cells, which rest on a very thin basement membrane. Small openings called stomata sometimes connect one alveolus with its neighbors. The walls contain both smooth muscle and elastic tissue and are exceedingly vascular. The vessels are capillaries with definite endothelial walls, and they form a network completely surrounding the alveoli.

The lymphatics have their beginnings as small intercellular spaces in the alveolar walls. These connect with larger lymph spaces in the interlobular septa, which then empty into definite channels also having endothelial linings. These latter channels are found in three sets which are called, according to their location, perivascular, peribronchial, and subpleural. The larger channels have valves and foci of lymphoid tissue distributed along their courses. They all terminate finally in the peribronchial nodes.[2]

Most text books on general pathology discuss the process of anthracosis, but they do not enter into a description of the steps by which the condition develops. We have based our conception on the study of a great many lungs in the various stages of the anthracotic condition, and a description of the appearances of lungs in these var-

ious stages will serve to explain how we reach our conclusions.

The finding of free carbon particles in the alveolar spaces was unusual, though in some of the very advanced cases black pigment masses filled some of the alveoli in such a way as to resemble a complete cast. In the early stages of the anthracotic process, the condition was manifested only by the presence within the air sacs of large round mononuclear phagocytes filled with carbon pigment, while in the slightly more advanced stages these cells were not only present in the alveoli but were also found in the interalveolar lymph spaces, in lymphatics of the interlobular septa, in those about the vessels, and beneath the pleura, and in those of the lower layers of the bronchial mucosæ. A little later these cells were found gathered in nests of considerable size, and many of them were seen to be compressed into spindles so that only the elongated nests of granules were visible. The very advanced conditions consisted only of a quantitative increase in all of the features mentioned above and if one examines a lung in a late stage of anthracosis, such as we have commonly observed in Pittsburgh, the following points will be noted: The deep layers of the bronchial mucosa may or may not show pigment bearing cells, and when they are present they are generally grouped about the small mucosal vessels. The alveoli contain pigment casts, pigment bearing phagocytes and rarely free pigment particles. The phagocytes are found in the lymph spaces between the alveoli, about the vessels, in the septa, and beneath the pleura, and those about the vessels are so numerous as to form rosette-like nodules consisting of alternate layers of pigment cells and of connective tissue trabeculæ (Figs. 1 and 7). The amount of connective tissue may be out of proportion to the number of pigment cells present. The striking point in the whole picture is the extensive plugging and obliteration of the small and medium sized lymphatics and the compression of the large

ones. In the pleura and in the peribronchial lymph nodes the picture is a similar one, and in the latter the lymphoid tissue is often completely replaced by a scar tissue, the meshes of which are full of pigment spindles. By following the findings from stage to stage, the process appears to consist in the taking up of the carbon pigment by cells in the lung alveoli and its transportation through the lymph spaces and channels to the peribronchial lymph nodes. During the process of transportation many of the pigment cells appear to be caught in the lymph spaces causing a backing up of similar cells in the spaces behind them. Here the cells seem to act as irritants and cause the proliferation of connective tissue, which holds them firmly. The nodules appear to be formed by the alternate blocking of small perivascular lymph spaces by pigment bearing cells and the formation of new spaces about the outside of the occluded ones. The new spaces then seem to become obstructed by the pigment cells in a similar way and so on until the concentric nodular anthracotic rosette is formed. The cells nearest the center are always more flattened and spindle shaped than those in the periphery. The continuation of the process over a long period of time leads gradually to a very severe embarrassment of the lymphatic drainage of the lung. It seems well to observe here that the separation of anthracosis by some authors into diffuse and nodular forms is one of degree only, as the condition which is diffuse in the early stages becomes nodular in the later forms.

Four very interesting questions arise in connection with the anthracotic process which we have up to the present purposely omitted from the discussion, because they seemed to be sufficiently important to deserve consideration under separate headings.

1. The question of the part played by the alveolar epithelium in the phagocytosis of pigment. Several authors state that the epithelial cells of the lung take up anthracotic pigment and that the pigment bearing cell is merely a desquamated alveolar lining cell. The author

devised a combined staining method based on Heidenhain's hematoxylin as a nuclear stain, in combination with Mallory's aniline blue connective tissue method, which brought out the epithelial lining cells of the alveoli as clearly defined cells with red protoplasm and dark brown nuclei, resting upon a pale blue basement membrane. This stain was applied to sections from two hundred anthracotic lungs, and no pigment granules were found in the attached epithelial cells (Figs. 3, 4). After they had become desquamated it was difficult to identify the epithelium from other mononuclear cells present, except in certain instances where the desquamation occurred in strips of several cells, attached end to end. In none of these instances were epithelial cells seen to contain pigment.

While not wishing to state definitely that epithelial cells cannot and do not take up pigment under some conditions we have no hesitation in saying that it is not the usual procedure and that we must look to other sources for the identity of the common pigment phagocyte.

2. Concerning the question of the identity of the pigment phagocyte. Beitzke[3] says that the pigment phagocyte is sometimes derived from the alveolar epithelium and at others is a wandering mononuclear white cell from the blood. Other authors have described them as endothelial leucocytes, those cells formerly called transitional and large mononuclear leucocytes which have been shown to come from the endothelial lining of the blood and lymph spaces.[4] We were able to get no specific stain to definitely settle this point. However, the pigment phagocyte observed in the alveolus and the endothelial leucocyte have many points in common. They are indentical in size and appearance, they are both phagocytic, for blood pigment, as well as coal pigment, they both take up all kinds of cells and cellular debris and lastly we will show—later that the pigment phagocyte and the early cell of the tubercle, which we believe to be an endothelial cell, is one and the same cell.

By injecting pigment, in the form of Higgin's India
ink, diluted one in five with normal saline we have at-
tempted to determine the indentity of the cells which
acted as phagocytes.

Experiment III.—Guinea-pig 2. Two cubic centimeters of
dilute India ink was injected beneath the scapula at 5 P. M. The ani-
mal was found dead at 8:30 A. M. on the following morning, and
presented the appearance of having died some hours before. Macro-
scopic description: The subscapular region was found much black-
ened and the neighboring lymphatics were deeply injected with black
pigment. Microscopic description: In the sections many polymor-
phonuclear leucocytes were present in the region and a few of them
contained a scant number of granules of pigment. A relatively few
endothelial leucocytes were present, but all of them contained abund-
ant granules.

Experiment IV. A similar dilute ink injection was made into
the interstitial tissues of the abdominal walls of a guinea-pig. The
animal was autopsied at the end of twenty-four hours. Macroscopic
description: There was present in the tissues of the abdominal wall
a localized nodule of swollen, edematous, and blackened tissue from
which both smears and sections were made. Microscopic descrip-
tion: Both smears and sections showed a considerable number of
endothelial leucocytes, and all of them contained a great number
of pigment granules. There was a very marked polymorphonuclear
leucocytic exudate present, but only occasional leucocytes were found
containing pigment granules (Fig. 6).

Experiment V.—This experiment was similar to the preceding,
save that the injection was repeated at the end of twenty-four
hours. The animal was examined at the end of forty-eight hours.
Macroscopic description: The gross appearance of the abdominal
wall was similar to that in the preceding experiment. Microscopic
description: A severe local endothelial leucocytosis was shown in
the sections and most of these cells contained pigment. Many poly-
morphonuclear leucocytes were also present, but the phagocytosis
of the pigment by these cells was insignificant.

It appears from these experments that the poly-
nuclear leucocytes may take up pigment, but that their
action is transient and unimportant, while the observa-
tions point to the endothelial leucocyte as the chief pig-
ment phagocyte of the body.

3. The length of time during which the enclosed pig-
ment remains intracellular is very important. As we have
described above, the pigment bearing cells often become
caught in the lymph spaces and when they have been sur-
rounded by scar tissue appear simply as pigment spindles
and look like nests of free granules, or as if they were
incorporated in spindle shaped connective tissue cells

(Fig. 7). In acute inflammation of the lung, and more particularly in edema, the spindles again assume a more or less round or oval form (Fig. 8), suggesting that the spindle shape is due entirely to the pressure of the scar tissue. In two experiments we were able to reproduce the condition.

Experiment VI.—A small amount of dilute India ink was injected interstitially into the ear of a rabbit. At the end of twenty-six days sections were made. Almost all of the pigment had been taken up and was found in the form of spindles firmly fixed between strands of connective tissue (Fig. 9).

Experiment VII.—The ear of another rabbit was treated in a similar way. After forty days the ear was dipped into water at 60° C. for three minutes. At the end of fifteen hours a very extensive edema of the ear had developed and the animal was brought to autopsy. Sections showed a very extensive interstitial serous-exudate, without any cellular elements, to separate the strands of connective tissue very widely. Almost all of the pigment was found to be present in cells which were of the large round type (Fig. 10).

In some processes within the lung, such as abscess, gangrene, the various granulomata, and tumors, which are accompanied by necrosis, the anthracotic pigment is found extracellular and is seen widely distributed as free granules. These granules sometimes remain free in caseous areas, or in scar tissue, or they may again be engulfed by large mononuclear phagocytes. From our own observations we feel justified in saying that carbon pigment once taken up by the cells remains intracellular indefinitely, unless freed by some process producing general necrosis of the tissues.

4. How long do phagocytic cells remain free in the alveoli? There is at present no accurate means of determining the length of time during which a cell may remain free in the alveolus, though there are several points which indicate that this is longer than is generally supposed. One may observe many cells in the lung alveoli which are only partially filled with pigment, but to find such a one in the intra-alveolar lymph spaces is quite unusual. This suggests that the phagocytic cells are generally pretty well loaded when they leave the alveoli.

In pneumonia and edema of the lung where individuals have been confined to the hospital for some time and presumably not inhaling very much pigment, the alveoli often contain numerous pigment bearing phagocytes. The almost constant presence in the alveolar spaces of "Herzfehler Zellen" in brown induration of the lung is hardly a terminal condition, and establishes further evidence that phagocytic cells may remain free in the alveoli for a considerable length of time. In Experiment II. we found that although the soot inhalations had been carried on for eighty-seven days, pigment bearing cells were found only in the alveoli and inter-alveolar spaces and there was no evidence that any had migrated as far as the large lymphatics. All of these points seem to indicate that the phagocytic cells are not transient scavengers, but in a more leisurely manner gather their pigment-load and transport it to the tissue spaces.

Summarizing the foregoing work we conclude:

1. The quantity of pigment taken up by the upper air passages is a negligle one.

2. The lining cells of the lung alveoli take little or no active part in the phagocytosis of carbon pigment.

3. The process consists in the phagocytosis of the pigment within the lung alveolus by a cell, which is probably an endothelial leucocyte. This cell then passes into the pulmonary lymphatics where it sometimes lodges and becomes surrounded by connective tissue. The pigment remains intracellular until acted upon by some process producing a local necrosis of the tissues.

4. The importance of the sequence of the process lies in the fact that the lymphatics of the lung become obliterated either mechanically or by fibrosis.

II.   The association of anthracosis and tuberculosis.—Pulmonary tuberculosis in adult individuals in Pittsburgh is constantly associated with more or less anthracosis, so that ample opportunity was afforded for the study of the effect of the one upon the other. The important lesion of tuberculosis is the tuberculous granuloma

or "tubercle," and the following discussion is confined to a consideration of the related lesions of this characteristic tuberculous lesion, and anthracosis.

The present day knowledge of the histogenesis of the tubercle is the result of the accumulated work of more than a generation of pathologists. Point by point has been added year by year, and credit cannot be given to any single individual or group of individuals, and more especially is this true for the reason that our facts are still deficient in certain details. The names of Baumgarten[5] working in Germany and of Borrell[6] in France, however, stand out prominently among the founders of the experimental studies, to which we owe so much. The formation of the tubercle as we understand it at present, seems, in general, to occur in the following way:

When tubercle bacilli enter the smaller vessels or lymph spaces they are shortly incorporated by the cells[o] lining these structures. In both blood vessels and lymph spaces the process appears the same so that the description of the former will suffice. The cells which have taken up the tubercle bacilli undergo rapid proliferation and develop a nest of proliferated endothelial cells which tends to fill the vessel, obliterate it, cut off the nutrient supply to the nest, and leave it an extra-vascular structure. The endothelial cells have by this time changed their morphology and somewhat resemble epithelial cells, for which reason they have long been known as "epithelioid" cells. About this time a few polymorphonuclear leucocytes may frequently be seen in the margins of the structure, but, in the later stages, lymphocytes alone are present. The next change which is usually observed is the appearance, near the center of the nest, of a multinucleated or giant cell, which was described by Langhans in his early studies on tuberculosis and to which his name has been given. That the Langhans' giant cell is the product of the endothelial cell seems now to be unquestionable, but a considerable dispute still exists as to whether it arises by a fusion of the endothelial cells or by a division of the nucleus

without a multiplication of the cell. Caseation necrosis is next seen near the center of the nest and commonly first manifests itself in the center of the giant cell. With the appearance of caseation there is not uncommonly a proliferation of connective tissue about the margin which is an attempt on the part of the tissues to encapsulate the lesion. This completes the structure of the miliary tubercle (Fig. 15). Complete encapsulation and healing may follow with more or less absorption of the necrotic matter by the tissues,[p] or the deposit of calcium salts within the caseated areas. On the other hand a local or general spread of the tuberculous process may follow. A certain amount of local invasion from the original tubercle may take place by direct extension leading to the development of numerous closely aggregated and fused tubercles. The lesion thus produced is known as a conglomerate tubercle. A more extensive local spread, even to the involvement of an entire organ, often takes place by way of the anastomosing lymph spaces.

Recently, considerable evidence has been advanced to show that the so-called epithelioid cells are at all times endothelial cells, and if this is true the term "epithelioid," which is somewhat confusing, should be discontinued. Mallory has called attention to the constant involvement of endothelial cells in the earliest recognizable lesions of tubrculosis, and has shown that no fibrils are demonstrable by stains in the tubercles until the stage of encapsulation is reached, at which time fibrils appear in conjunction with the proliferating connective tissue cells in the outer border. Since endothelial cells are not known to produce fibrils, the evidence is in favor of the essential cell of the tubercle being endothelial in character. Bowman, Winternitz, and Evans have shown experimentally that tubercles may be developed in the liver from the Kupffer stellate cells, which are also considered as endothelial cells. By first inducing a vital staining of these cells in animals by injecting trypan blue into the circulation, then inoculating the same animal with tubercle bacilli, they

were able to follow the formation of tubercles by the stained cells. I have also induced the development of tubercles experimentally, the essential cells of which were phagacytic both for pigment granules and the tubercle bacillus (Experiments VIII., and IX., and X., and Figs. 17, 18, and 19), and if we were right in concluding that the endothelial cell is the general pigment phagocyte of the body, we have another link in the chain which indentifies the "epithelioid" as an endothelial cell.

As to the nature of the Langhans' giant cell we have, in several instances, observed multinucleated cells containing both pigment granules and tubercle bacilli. This would indicate that the cells exhibiting the phagocytic properties to foreign particles and tubercle bacilli were of the same origin and that the giant cells were but a morphological modification of these. As to the way in which the phenomenon of multinucleation occurs we have no conclusive additional evidence. An experiment was planned by which it was hoped to discover a constant ratio between the amount of pigment taken up and the number of nuclei present in the giant cell. The experiment failed, firstly, because time was not allowed for complete phagocytosis of the pigment before the tubercle bacilli were introduced and, secondly, because the amount of pigment used was so great as to completely obscure many of the nuclei in the cells. The experiment though unsuccessful seems worthy of repetition.

Lesions illustrating the association of the various stages of tubercle formation with all degrees of anthracosis were found in the materials secured from the autopsies and the following interesting observations were made: (1) Examples of early tubercles were found which consisted of simple nests of endothelial cells, some of which contained black pigment granules though they differed apparently in no other way (Fig. 16). (2) Pigment granules were found in many of the giant cells, and when caseation necrosis was also present in these cells the nuclei were found arranged in the periphery with the

pigment granules grouped in circles about them (Fig. 20). (3) In tubercles where caseation was advanced much of the pigment was found to have been liberated and occurred either as free granules diffusely distributed throughout the necrotic foci or, as was more often the case, gathered in the margins of the caseous areas where it was found undergoing a second phagocytosis by endothelial cells (Fig. 21). (4) Many partially and completely encapsulated tubercles were seen with great numbers of pigment spindles caught in the meshes of the capsules, and in these instances the connective tissue was unusually abundant. Obliteration of the neighboring perivascular lymph spaces by anthracotic fibrosis was a common additional finding in some of these lesions.

The number of cases examined was too small to allow the drawing of a general conclusion, but it seemed that there was less local spread and more extensive fibrosis in this latter type with anthracosis than is usual in ordinary pulmonary tuberculosis. It further seemed that the presence of pigment within the endothelial cells did not interfere with their development of typical tubercles (Experiments VIII., IX., and X.).

Experiment VIII.—Two cubic centimeters of a very dilute suspension of India ink was shaken up in normal salt solution with two loops of bacillus tuberculosis bovinus (kindly furnished by Dr. W. L. Holman) and was injected into the deep muscles of the thigh. After twenty-four days the animal was killed with chloroform and autopsied. Macroscopic description: Indefinite grayish-black tubercle-like nodules were found among the muscle fibers, and some of the intermuscular lymph spaces appeared as blackened lines. There was no evidence of involvement of the inguinal nodes, nor of the other organs or tissues of the body. Microscopic description: Many early tubercles were seen in the process of formation and the cells composing them often contained black pigment granules (Fig. 17). Tubercle bacilli and these pigment granules were repeatedly found in the same cells. Relatively few multinucleated cells were seen, but in some of them bacilli and pigment granules were found together. Practically no fibrous proliferation was present about the lesions and the cells did not show any kind of fibrils when special stains were applied.

Experiment IX.—One cubic centimeter of a I in 5 suspension of India ink in normal saline was shaken up with two loops of bovine tubercle bacilli and injected underneath the scapula of a rabbit. Ten days later inhalations of soot similar to those used in Experiment II were begun. These were carried out about every five days

and about fifteen inhalations were given. After seventy-four days the animal died from general tuberculosis. Macroscopic description: A large caseous mass about 4 centimeters in diameter,[p] near the center of which was a small black nodule was found beneath the scapula. The lungs, liver, spleen, and kidneys showed very advanced caseous tuberculous lesions. A few rather indefinite black granules appeared about the margins of the lung tubercles. Microscopic description: The lungs alone are of interest in this experiment. They contained all stages of tuberculous lesions, and a few fine pigment granules were observed in some of the cells forming the tubercle. Two vascular lesions were of interest because they showed direct extensions of early tubercles into the lumina of vessels without causing rupture of the walls. The subscapular lesion was in a very advanced stage of caseation necrosis and was valueless for study.

Experiment X.—Injections as carried out in Experiment VIII. were made into the interstitial tissue of a rabbit's ear. The animal was brought to autopsy at the end of twenty-six days. Macroscopic description: The ear showed one large diffuse black area involving approximately one-half of the ear. The tissues were somewhat thickened and contained three large and several small grayish-black nodules. At the base of the ear was found an enlarged and blackened lymph node. Microscopic description: Sections of the ear and lymph node both demonstrated the presence of early tubercles, with black pigment granules in the cells of the tubercle, and in both instances tubercle bacilli and pigment granules were found in the same cells (Fig. 19).

In all three of these experiments we were able to induce miliary tubercles,[p] formed by cells which were filled with pigment granules. This indicated that the presence of pigment in the specific cells did not exert any inhibitory influence to the development of tubercles. By demonstrating pigment granules and bacilli in the same cells of the tubercle, we were able to show that a single cell may actively phagocyte both materials. In other words, the essential cell of the tubercle and the pigment phagocyte were found to be identical. Still more interesting was the finding in Experiment X. in which both the pigment phagocytes and tubercle forming cells were found in a neighboring lymph node, where tubercles were being formed by cells which contained pigment.

Summing up our observations on the associated lesions of anthracosis and tuberculosis we came to four conclusions:

1. The cell which takes the early active part in the formation of a tubercle is phagocytic for tubercle bacilli

and for pigment granules and is probably an endothelial cell.

2. The presence of pigment granules within these cells does not interfere with the cells taking part in the formation of a tubercle.

3. The presence of pigment-bearing cells in the connective tissue about tuberculous lesions acts as an additional stimulus to fibrosis and encapsulation.

4. The obliteration of the pulmonary lymph spaces in the anthracotic process is unfavorable for the local spread of tuberculosis, and aids in the localization of the condition.

III. The association of pneumonia and anthracosis.—With pneumonia the relation of anthracosis is a very different one. The process is one of acute inflammation wherein the alveoli, bronchioles, and often the smaller bronchi become filled with a fibrino-purulent exudate. Ordinarily this exudate remains in the alveoli for a relatively short time, usually from five to nine days, and then undergoes resolution. The process of resolution consists, firstly, in a softening and liquefaction of the exudate, which takes place through the autolytic action of the different elements, and is known as puriform softening, and secondly, in getting rid of the resulting debris. Much of the resolved exudate is coughed up, but the greater part of it passes back into the circulation by way of the lymph spaces and through the lymph nodes.[7] During resolution these spaces are found to be dilated and to contain fluid, fragments of fibrin and many types of exudative cells. Among these cells are numerous phagocytes containing other cells, cell debris, fibrin, and fat globules (Fig. 13). The contents of the sinuses of the lymph nodes is exactly the same (Fig. 12). It is evident that for the removal of this debris as well as for active phagocytosis comparatively large channels are necessary, and it is obvious that anything which may impede the passage through the lymphatics must interfere with the healing process. The mechanical blocking of the spaces forces the debris to find

other channels of exit, and the imperfect drainage leads to the accumulation of waste products which, in turn, may retard the activity of the proteolytic enzymes.

When for any reason resolution of pneumonia fails to take place the microscopic picture presents certain characteristics. The cellular elements of the exudate are not numerous and are often lymphocytic; the fibrin becomes contracted into firm hyaline, spindle, or fan-shaped masses which are bathed in fluid, and the alveolar wall appears thickened and edematous. At somewhat later periods these fibrinous masses occasionally undergo organization in a way comparable to the repair of a wound. Abscesses are also very common findings in pneumonic lungs where failure of resolution has occurred, and gangrene is also seen in some instances. Not only are such lungs unusually susceptible to secondary infection, but the actual presence of the undigested fibrin is claimed to be extremely toxic.

Our evidence of the effects of anthracotic conditions on pneumonia was obtained by a microscopic study of sixty-two cases of the disease. Of these, thirty-eight were lobar, twenty were of the bronchial type, four were hypostatic, and two were the end result of general septicemia.

Of the thirty-eight lobar pneumonias, nine, or nearly twenty-five per cent., were diagnosed "unresolved" at autopsy and two others presented microscopical evidences of the same condition. Two of the bronchial type contained much hyaline fibrin and abscesses, and one of the hypostatic variety showed advanced organization.

This unusually large percentage of failures in resolution suggested a careful study of the pulmonary lymph spaces in these cases. This was carried out as far as we were able in the sections. Our attention was mainly directed toward the large channels because the small lymph spaces were obviously involved in all of the cases, and also because a severe involvement of the larger lymphatics indicated an extensive participation of the smaller contributory vessels over a considerable area. We found the

large perivascular and subpleural lymph spaces closed or compressed in four cases by anthracotic fibrosis. Two cases presented a similar picture save that the amount of scar tissue seemed to be out of all proportion to the number of pigment cells. One instance was found where the lymph spaces were closed by scar tissue alone, and in two others there was no local evidence which could be construed as having anything to do with failure of resolution. The two remaining cases were pneumonias in which there were coexistent septicemias, and were omitted from consideration because the origin of the lung abscesses might have occurred as a part of the general process. Both of these lungs were examples of late stages of anthracosis. Our results, then, showed that in six of the nine cases of unresolved pneumonia the larger lymph channels were severely embarrassed by the anthracotic process.

The failure of resolution in pneumonia is commonly attributed to the low state of the general bodily condition, although Pratt[8] called attention to the frequency of delayed resolution in individuals who had been previously attacked, and attributed it to the fibrosis of the lymph spaces following the lymphangitis which occurs during resolution.

The results of the microscopic examination of the lymphatics in the total number of lobar pneumonias were as follows: Eighteen cases presented dilated lymph spaces filled with serous or sero-purulent exudate; five were closed by acute fibrino-purulent exudate, nine were practically obliterated by anthracosis; two were obliterated by scar tissue, and four were in the stage of resolution with large numbers of phagocytes in the lymph sinuses.

An analysis of these findings seems to indicate that during an attack of pneumonia in an otherwise normal lung the lymph vessels are generally engaged in an active exchange of fluids. Even in those instances where these channels are filled with a fibrino-purulent exudate this

exudate has a better chance of becoming liquefied and returning to the circulation than a similar exudate in the alveoli. So that even under these circumstances they would again be available for drainage.

The presence of the phagocytes in the channels and in the sinuses of the lymph nodes shows fairly conclusively that the lymphatics are important drains during the stages of resolution of pneumonia, and if these are closed the waste products of autolysis of the exudate must accumulate, and such an accumulation undoubtedly interferes with proper enzymatic action. In several of the above mentioned cases where the lymphatics were found to be closed, death occurred before the stage of resolution was reached. It is, of course, impossible to say that the presence of the anthracotic condition had any definite connection with the fatal result. Yet it is likely that the lymphatics in inflamed areas are just as important for the entrance of fresh fluids as for the exit of waste materials. It has been variously shown that the cultures of pneumococci obtained from pneumonic lungs after crises are less virulent than those made in the early stages, and this suggests some immune reaction against the organisms. If we are correct in the supposition that immune substances are the products of the entire body as well as of local origin, we must recognize the need of a constant influx of fresh fluid containing such immune products. It seems, then, that the closed lymph spaces may have had some effect even in this latter class of cases.

Our series although small seems to point toward a certain relation between "unresolved pneumonia" and anthracosis with chronic obliterating lymphangitis.

An interesting collateral finding, brought out by the newly devised staining method used in demonstrating alveolar epithelium, showed that desquamation of alveolar epithelium in pneumonia is inconstant and occurs only in some alveoli. Instances were observed in which the pneumonia had reached a stage of resolution and yet practically all of the alveolar epithelium was intact.

1. Any process which interferes with the free lymphatic drainage during pneumonia will delay resolution, both by actual mechanical obstruction to the migration of cells, and by aiding in the accumulation of waste products probably embarrassing enzymatic digestion of the exudate.

2. Anthracosis is an important process in the lung interferring with lymphatic drainage, and is a factor in causing delayed resolution.

Summarizing the various points indicating the disease importance of anthracosis which we have gathered from histological evidence we draw the following conclusions:

1. Moderate anthracosis in an otherwise normal lung is not in itself detrimental to health.

2. In tuberculosis and granulomatous conditions in which the reactions are chiefly centered in focal lesions of the tissues, the anthracotic condition is either entirely passive, or is active in assisting healing, in that it is an additional stimulus to fibrosis and encapsulation and in that it aids in the localization of the process through the obliteration of the lymph spaces.

3. In acute inflammatory conditions where the lymphatics are important for proper resolution, anthracosis becomes seriously detrimental, because of the obliteration of these spaces.

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Description of Plates XIV-XVII

DESCRIPTION OF PLATES XIV-XVIII.

Plate XIV., Fig. 1.—Perivascular arrangement of nodular anthracosis.

Fig. 2.—Subpleural type of anthracosis.

Fig. 3.—Alveolus containing many pigment phagocytes and a pneumonic exudate. Note the alveolar epithelium swollen and free from pigment.

Fig. 4.—Alveolus containing pigment phagocytes with alveolar epithelium intact. Note one cell containing both pigment and a red blood corpuscle.

Plate XV., Fig. 5.—Experimental anthracosis. Pigment phagocytes in alveoli and inter-alveolar lymph spaces.

Fig. 6.—Injection of carbon pigment in abdominal wall. Pigment present in large round cells and in inter-cellular spaces. Polynuclears contain no pigment.

Fig. 7.—Spindle-like arrangement of pigment in perivascular anthracotic nodules.

Fig. 8.—Effect of edema on spindle-like pigment occlusions in perivascular anthracosis.

Plate XVI., Fig. 9.—Experimental fibrosis produced by the injection of India ink into a rabbit's ear.

Fig. 10.—Effect of artificially produced edema on rabbit's ear which had been treated in a similar way to that seen in the preceding figure.

Fig. 11.—Alveoli containing pneumonic exudate in stage of resolution. Note epithelial cells intact on alveolar walls.

Fig. 12.—Lymph spaces of peribronchial lymph node containing phagocytes from preceding figure.

Plate XVII., Fig. 13.—Perivascular lymph space filled with broken up fibrin and phagocytes from same case as preceding figure.

Fig. 14.—Perivascular lymph spaces completely obliterated by carbon pigment and fibrosis. From severe case of unresolved pneumonia.

Fig. 15.—Formation of early lung tubercle.

Fig. 16.—Early tubercles containing pigment bearing cells (human).

Fig. 17.—Experimental tubercle in rabbit's thigh. Pigment bearing cells actively forming the tubercle.

Plate XVIII., Fig. 18.—Oil immersion view of same tubercle. Cells contain both pigment granules and tubercle bacilli.

Fig. 19.—Tubercles containing pigment bearing cells in lymph node.

Fig. 20.—Arrangement of pigment in giant cells in late stage of tuberculosis.

Fig. 21.—Distribution of carbon pigment in the periphery of caseous tubercle.

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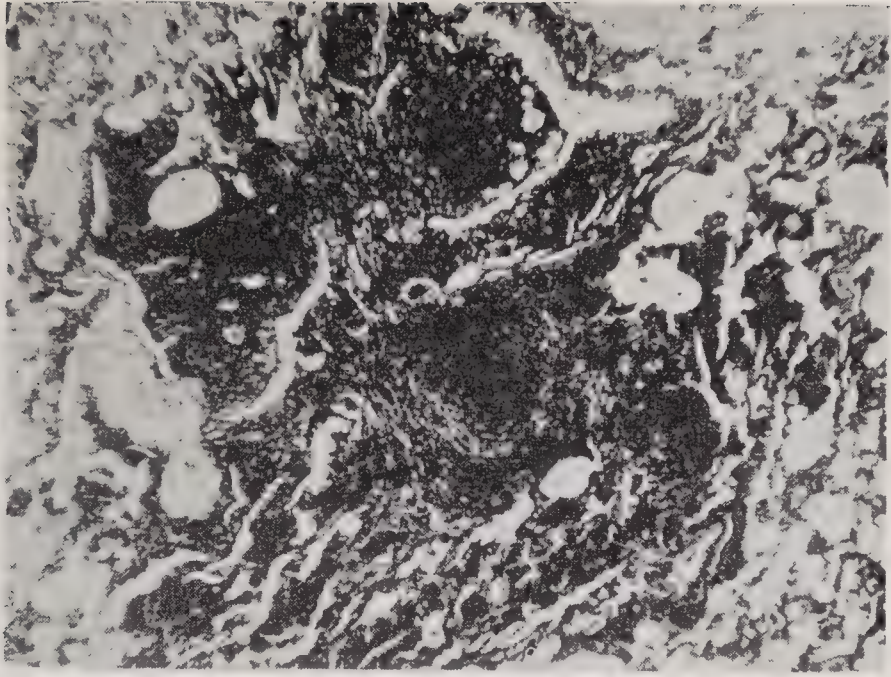
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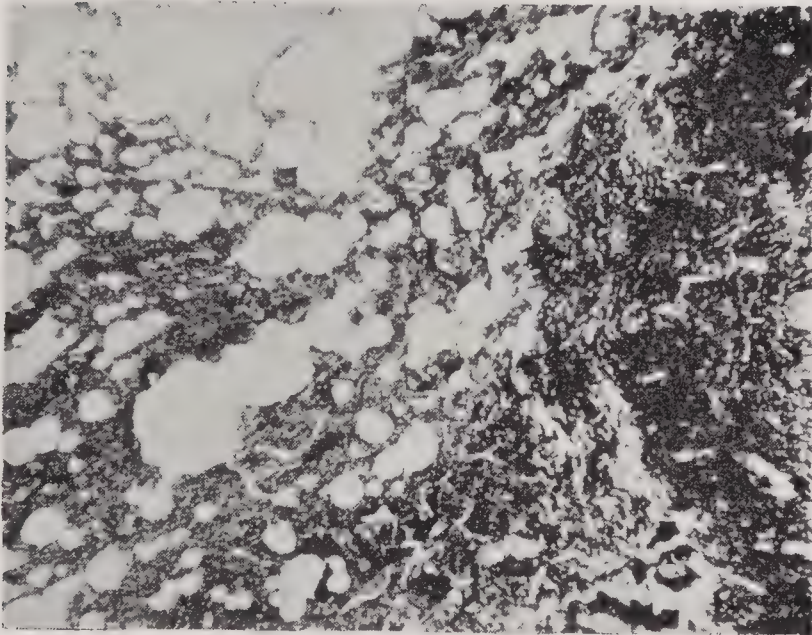
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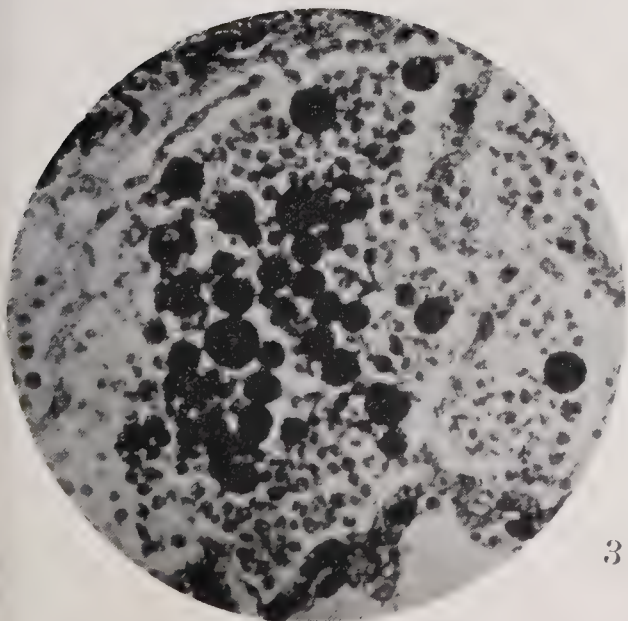
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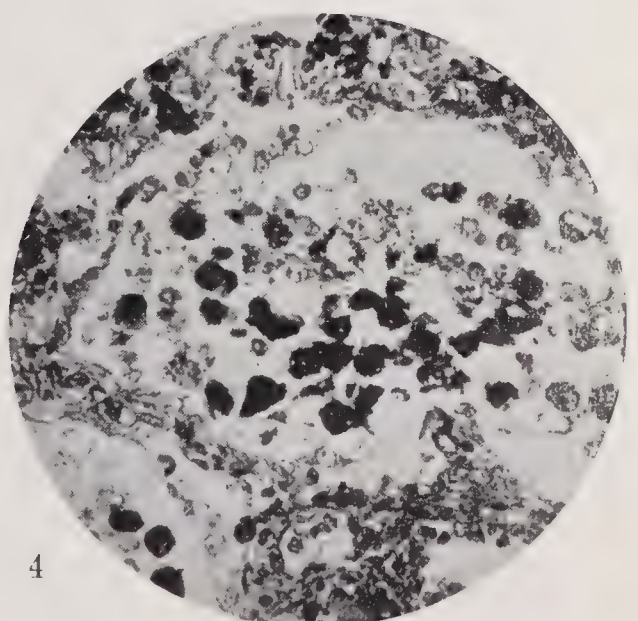
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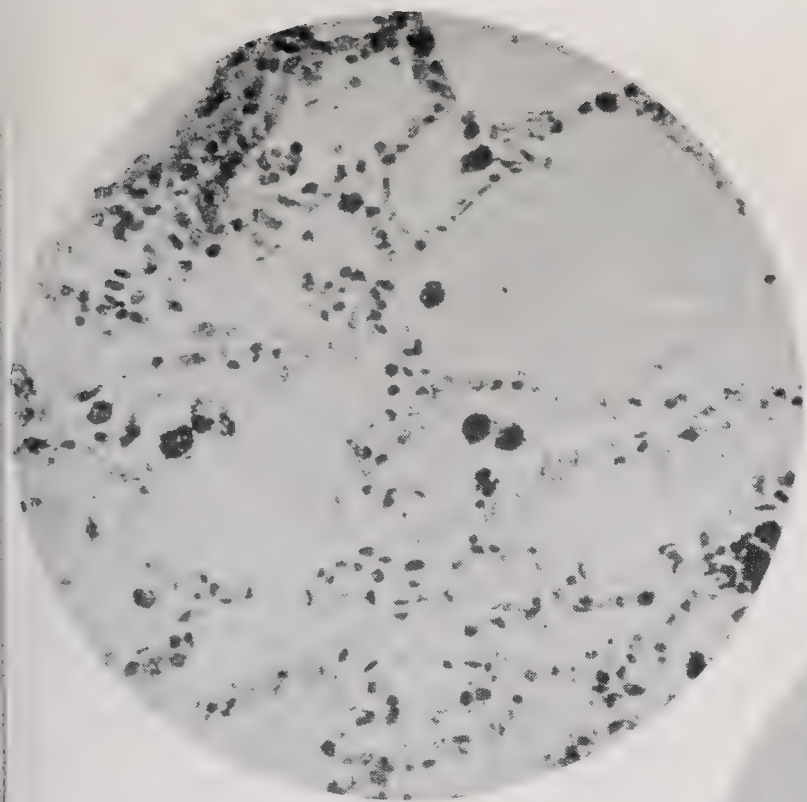
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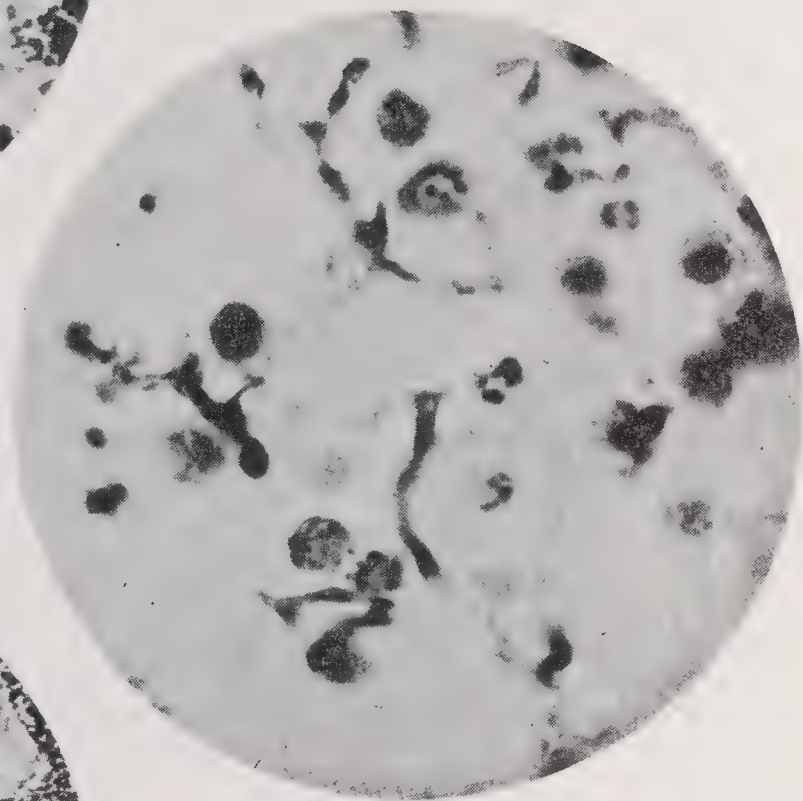
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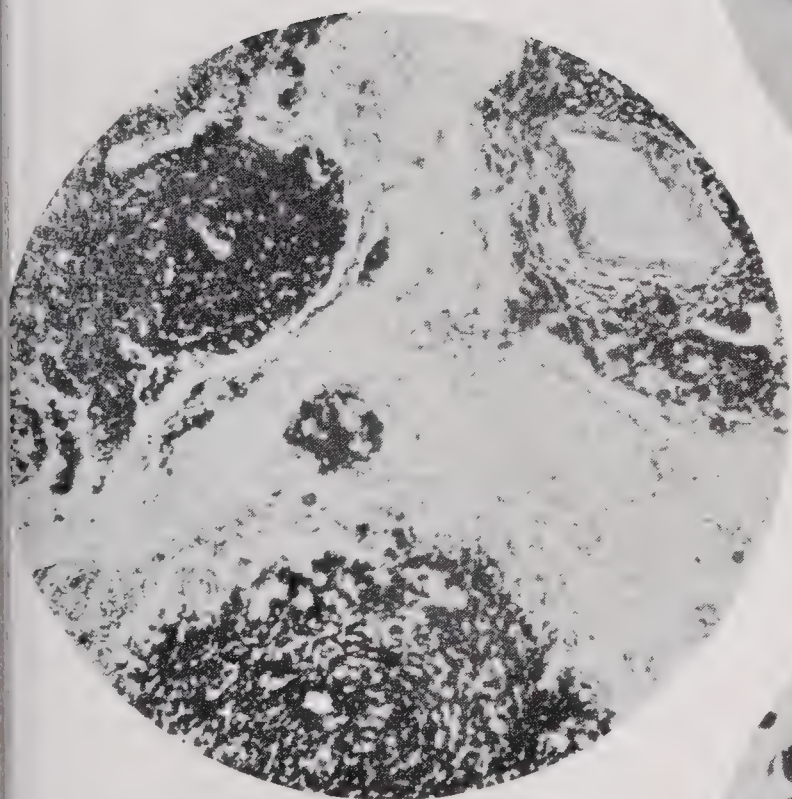
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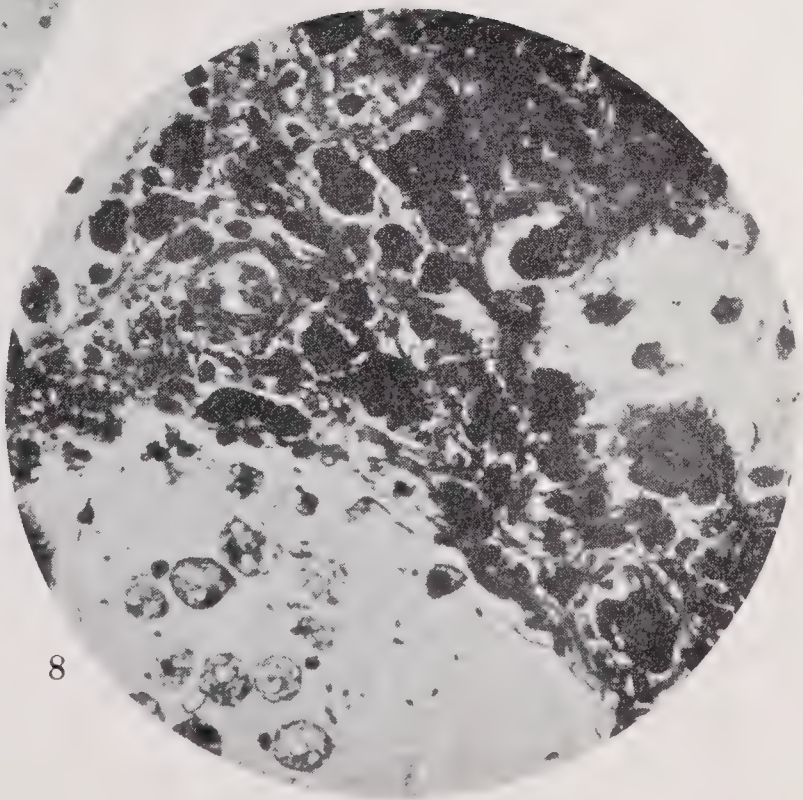
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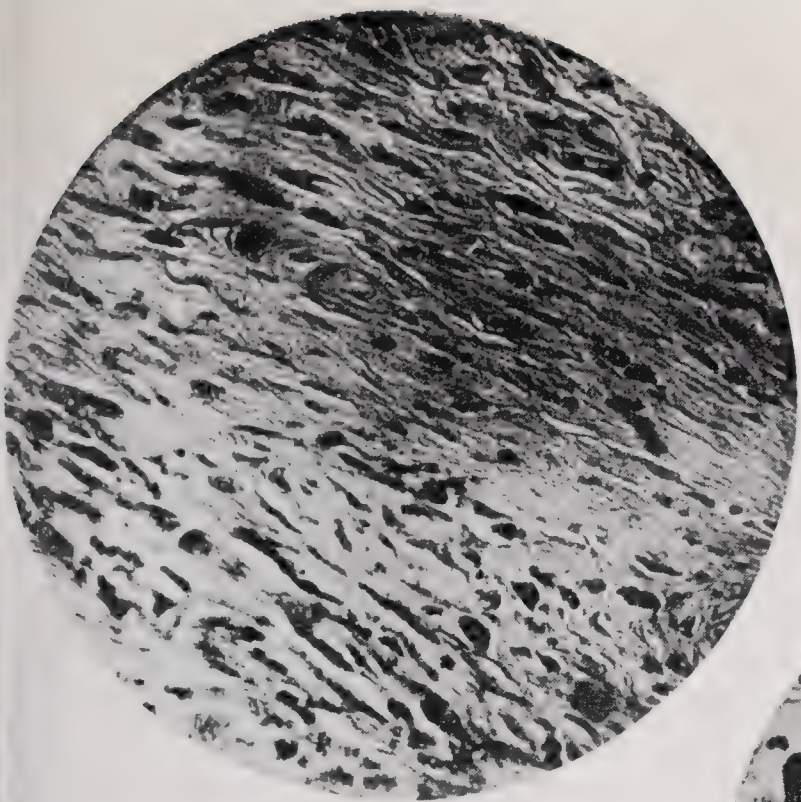
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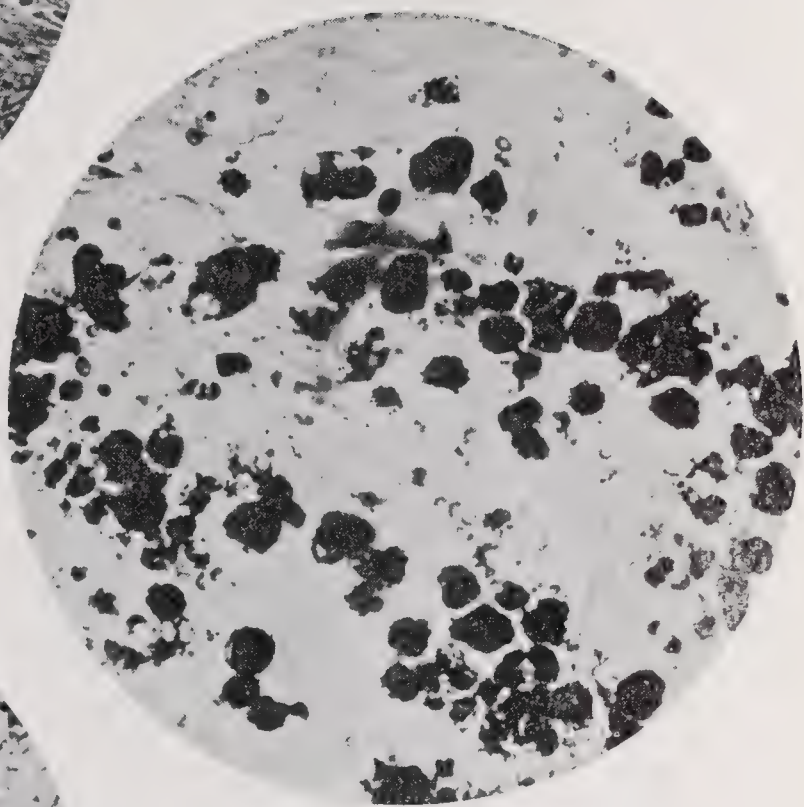
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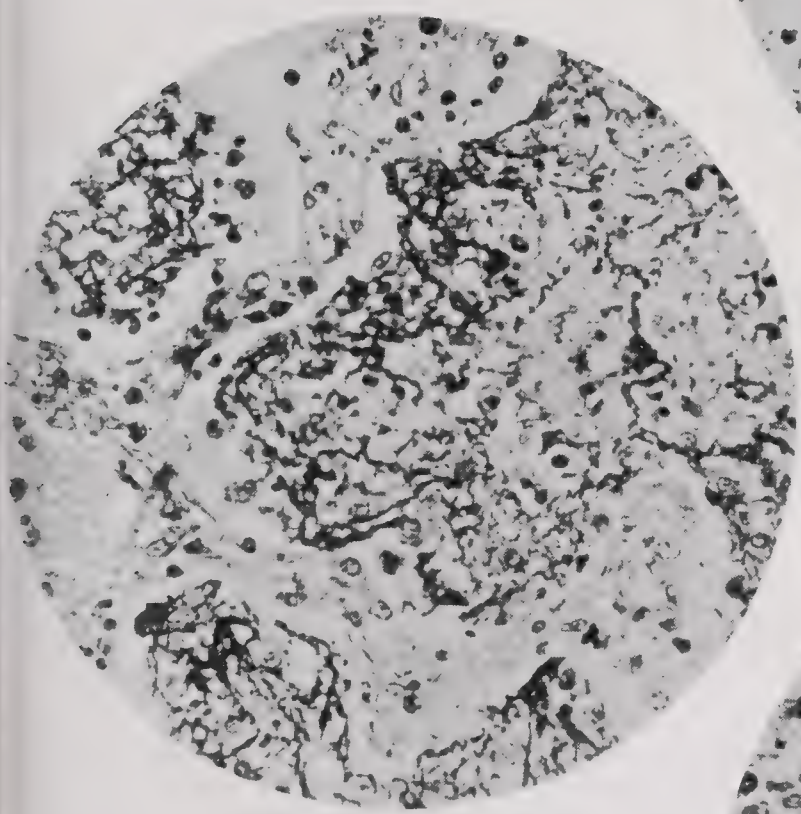
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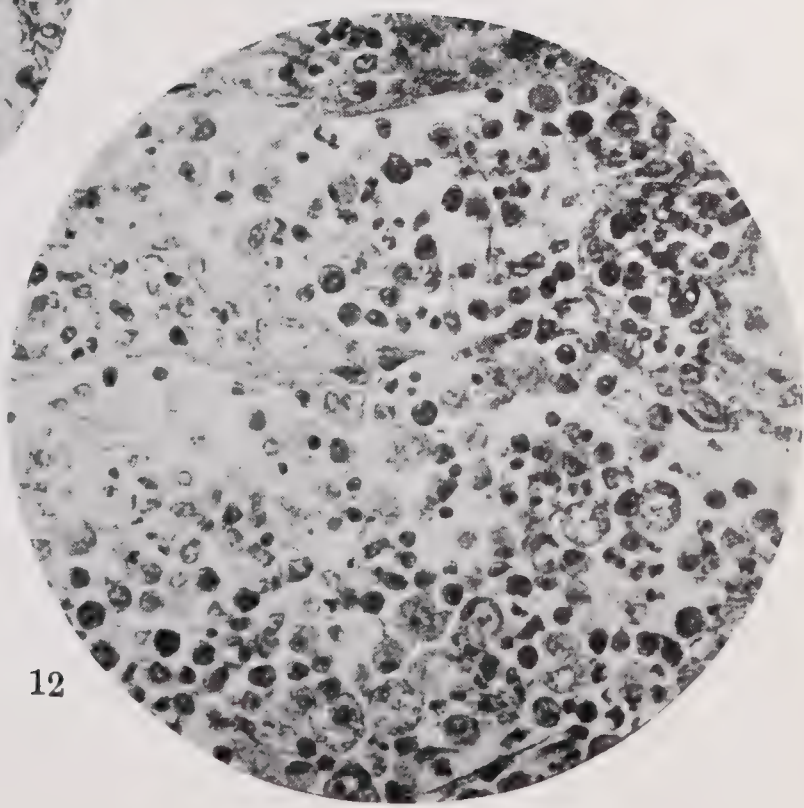
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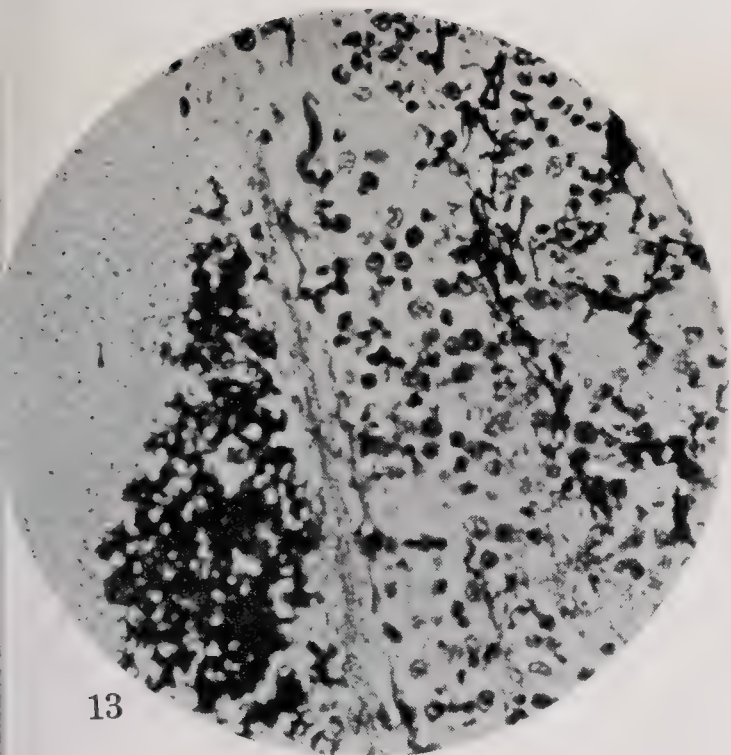
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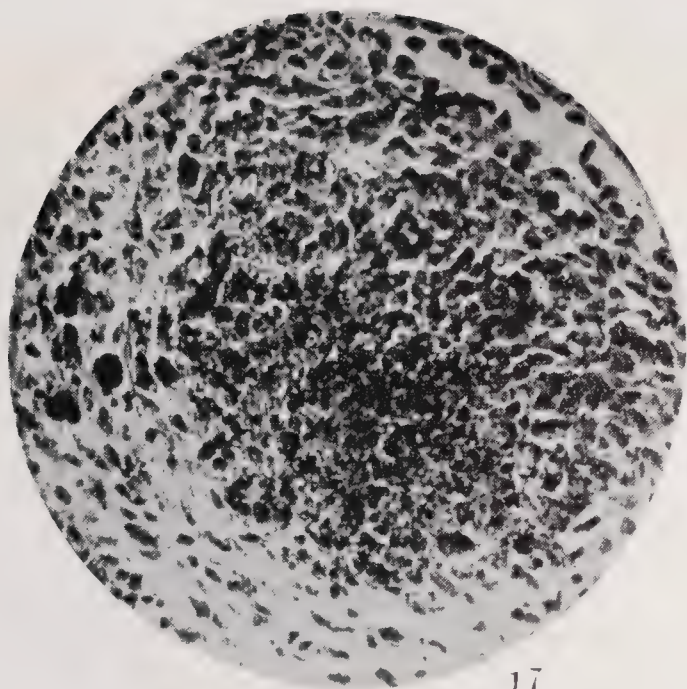
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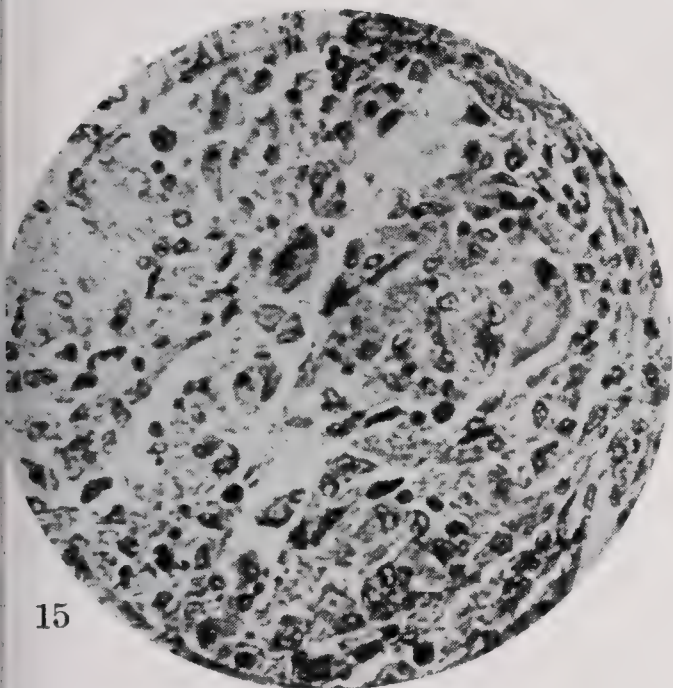
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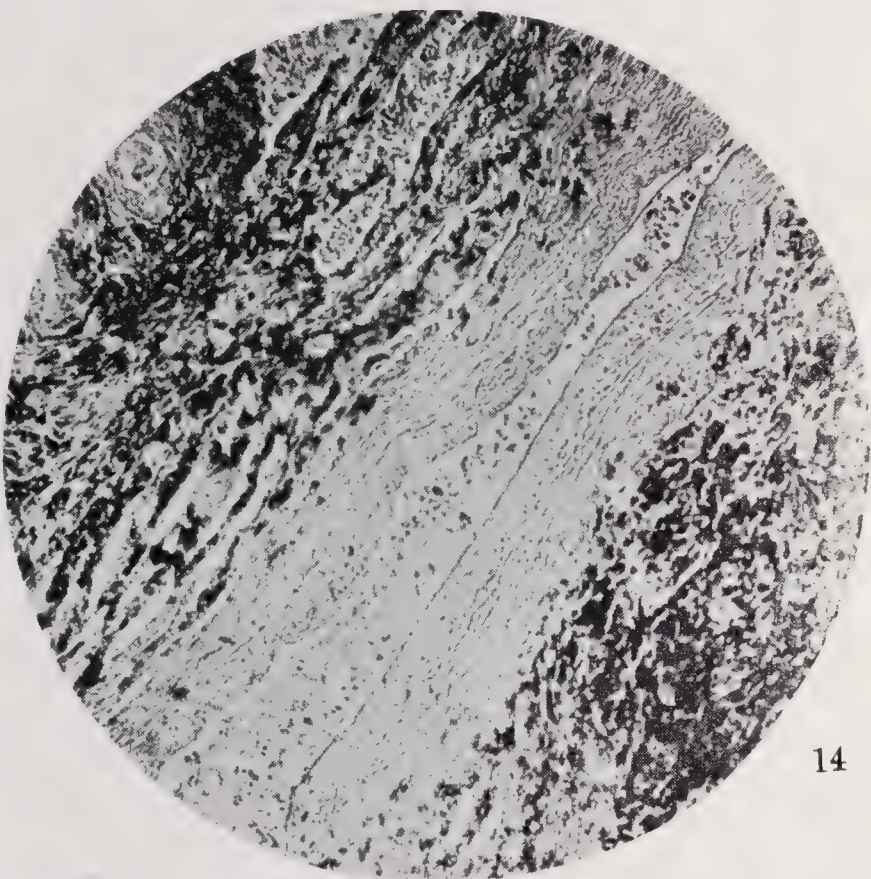
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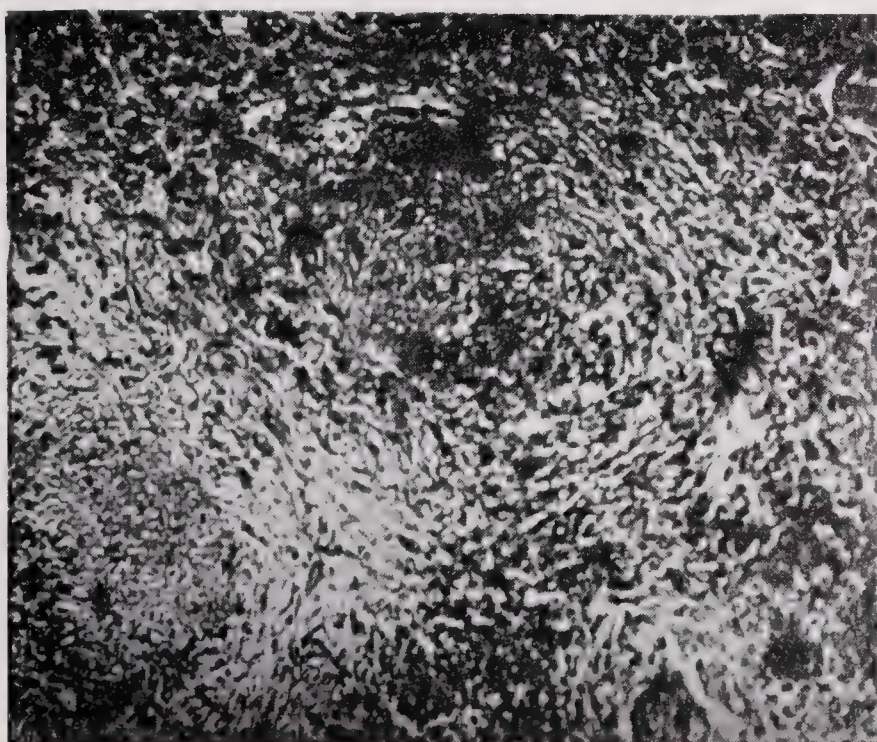
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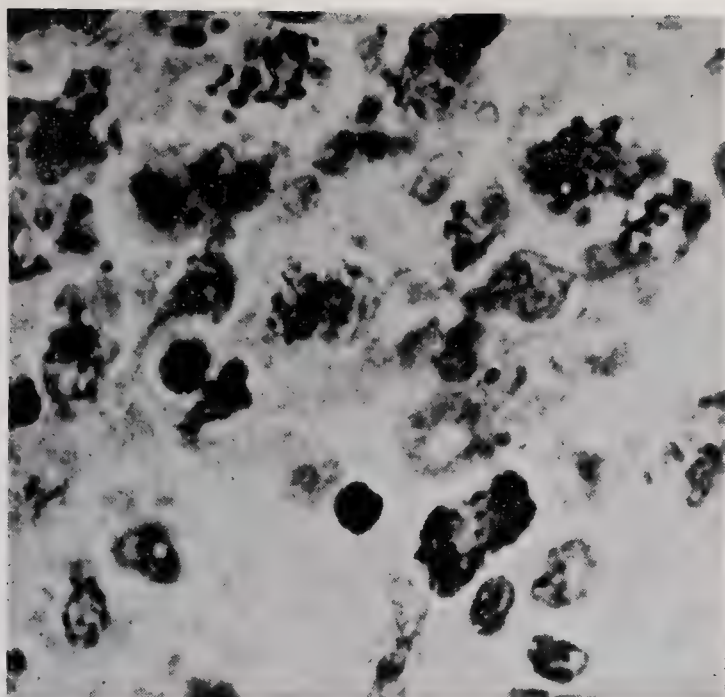
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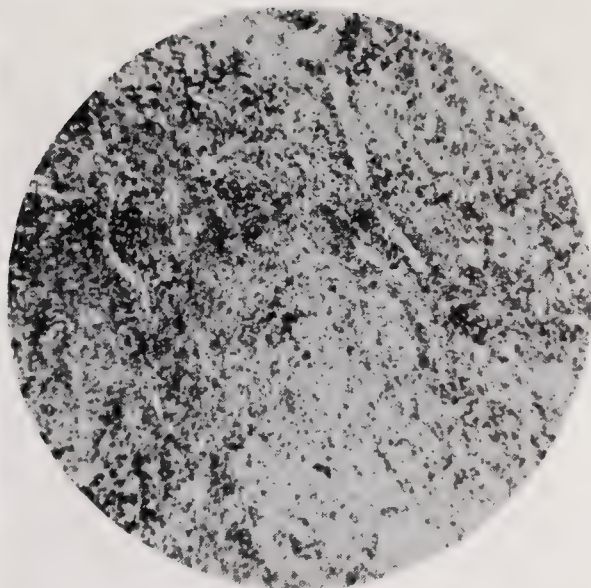
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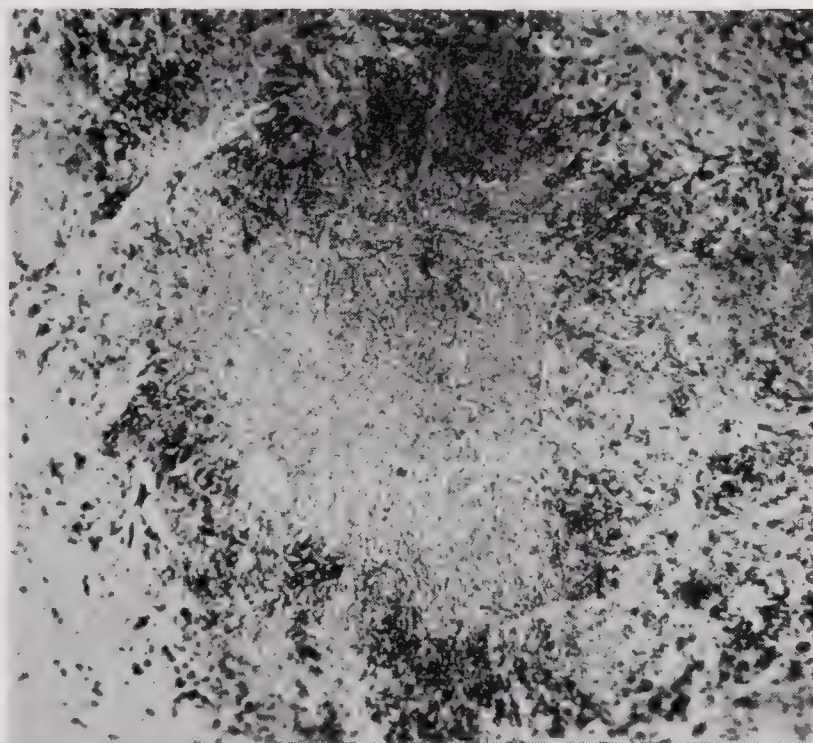
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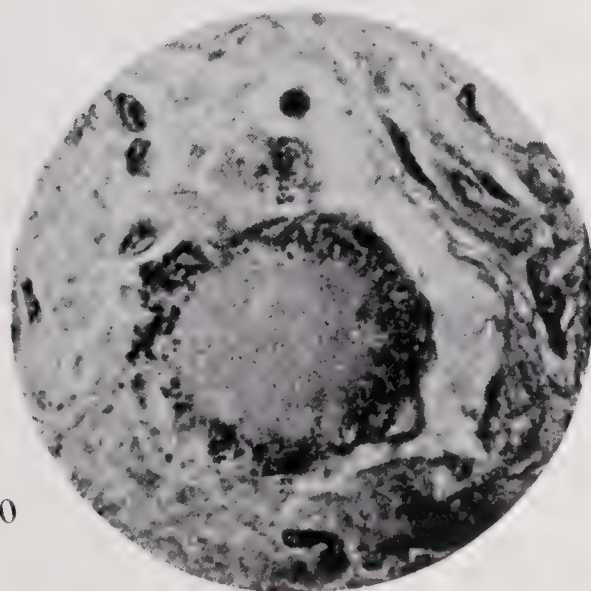
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A Study of the Influence of Varying Densities of City Smoke on the Mortality from Pneumonia and Tuberculosis*

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AND

C. H. MARCY.

As part of the investigation into the smoke problem, which is being carried on at the University of Pittsburgh, through the generosity of Mr. R. B. Mellon, we have made

Pittsburgh, Pa.
Showing Smoke Areas
by Wards

Chart I

COMPARISON OF TUBERCULOSIS DEATH RATE
BY WARDS AND SMOKE CONTENT OF AIR BY WARDS

●·■ Average Tuberculosis Death Rate   ■■ Average Soot fall per Month
per 1000 for Years 1909, '10 and '11   in gms.
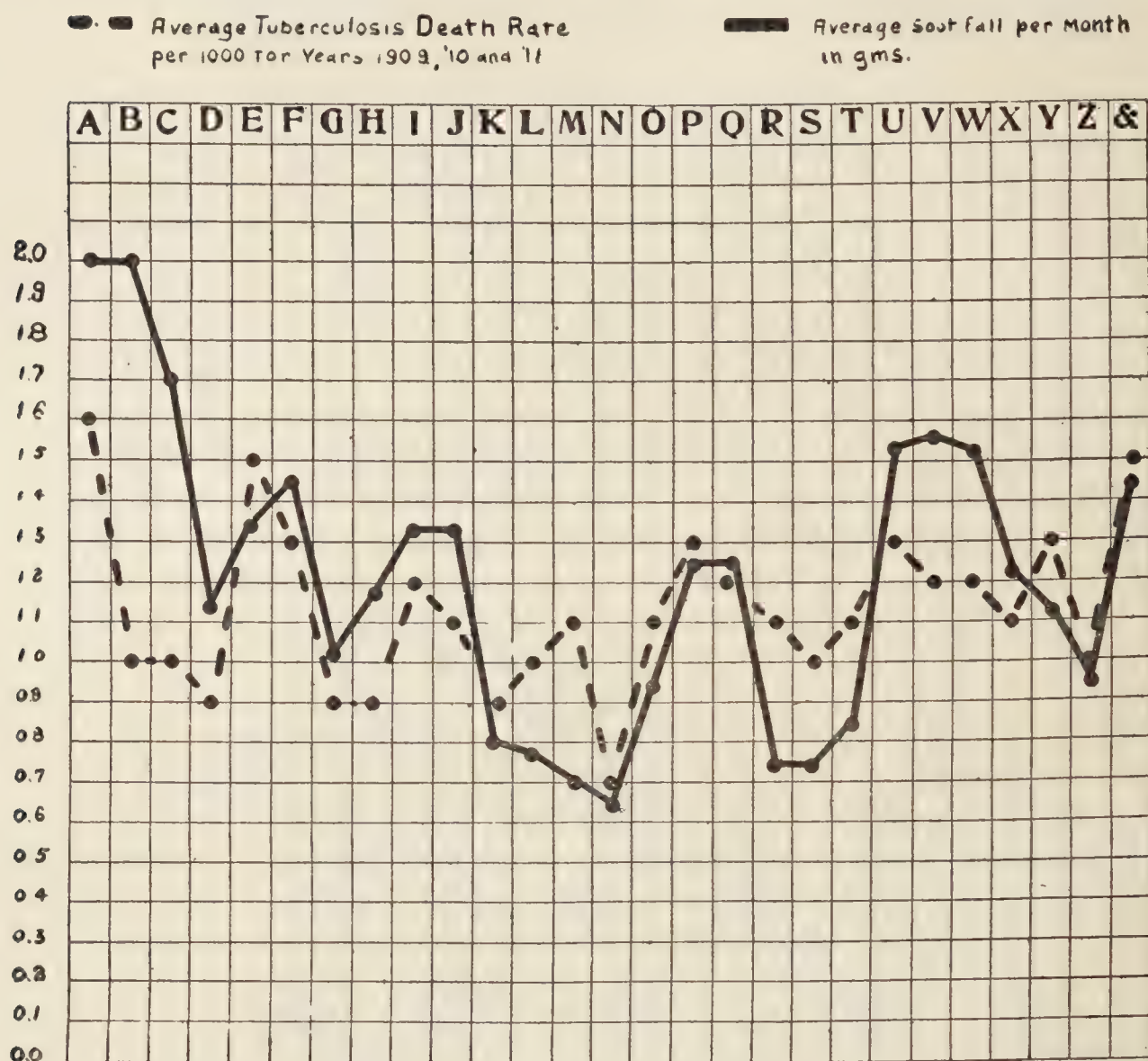
Chart II.

a study of the influence which varying densities of smoke
have on the mortality from tuberculosis and pneumonia
as typifying acute and chronic pulmonary infections. Per-
haps in none of the smoky cities of the world is it possible
to go into the influence of smoke in the same way as in
Pittsburgh. The peculiarity of the relation of high hills
and valleys, in close proximity, within the city limits,
makes a well-defined variation in the smoke content of the
air. It will be noticed on the map (chart 1) that, along
the river frontage, where for the most part the land is low-
lying, the air content of smoke is very dense; skirting this
dense smoke area, the hills rise more or less abruptly to

varying heights. On the lower hills, as exemplified by
C, D, E, J, Y, Z, and &, there is an area of moderate smoke
density. Where the hills, however, rise directly from the
river to the height of 400 or 500 feet, as exemplified by
R, S, T, G, K, L, N, and M, there is comparatively little
smoke at any time of the year. During prosperous times,
the valley, or dense-smoke area near the rivers, is always
heavily laden with smoke. This is true even when there
is a brisk breeze blowing.

It is possible, from the division of the city into wards,
to rule out a number of other factors, such as poverty, race
congestion, and so forth, as an influencing factor in the
point of relation which we have brought out by these
studies.

It is unfortunate that our figures only cover a period
of two years, but this is due to the fact that no records
taking account of the wards of the city have been kept
prior to this time and also that the number of wards was
changed from 56 to 27 three years ago. This renders use-
less any previous comparison on the ward basis.

The figures which we have obtained are, from one
aspect, very convincing, although from another aspect
very confusing. It will be noticed for instance, in Chart
4, that in Chicago, where there is a comparatively low
smoke content, there is still a very high pneumonia death
rate; while in Pittsburgh, with the highest smoke density,
there is no higher pneumonia mortality.

The question of smoke density for the various cities
has been based upon the reports of the United States Gov-
ernment Weather Bureau. In the various cities which
are included in this report the method of determining this
density is based on the distance of vision, considering cer-
tain fixed objects in the city from an observation center.
In Charts 2 and 3, of Pittsburgh, the basis has been certain
carefully devised studies of precipitation of air content of
carbon dust. These scientific observations have been made
in connection with the present smoke study by Messrs.
R. C. Benner and C. H. Marcy. In Chart 4, for the sake

of comparison, we have adhered to the Government Weather Bureau report.

The mortality tables, on which Charts 2 and 3 are based, were derived from the health table of statistics of the city of Pittsburgh, and include the years 1910 and 1911.

COMPARISON OF PNEUMONIA DEATH RATE BY WARDS AND SMOKE CONTENT OF AIR BY WARDS.

I ▬ Average Pneumonia Death Rate per 1000 for years 1910 and 1911

III ▬ Number of People per Here Rough indication of Poverty

II ▬ Average Soot Fall per Month in gms
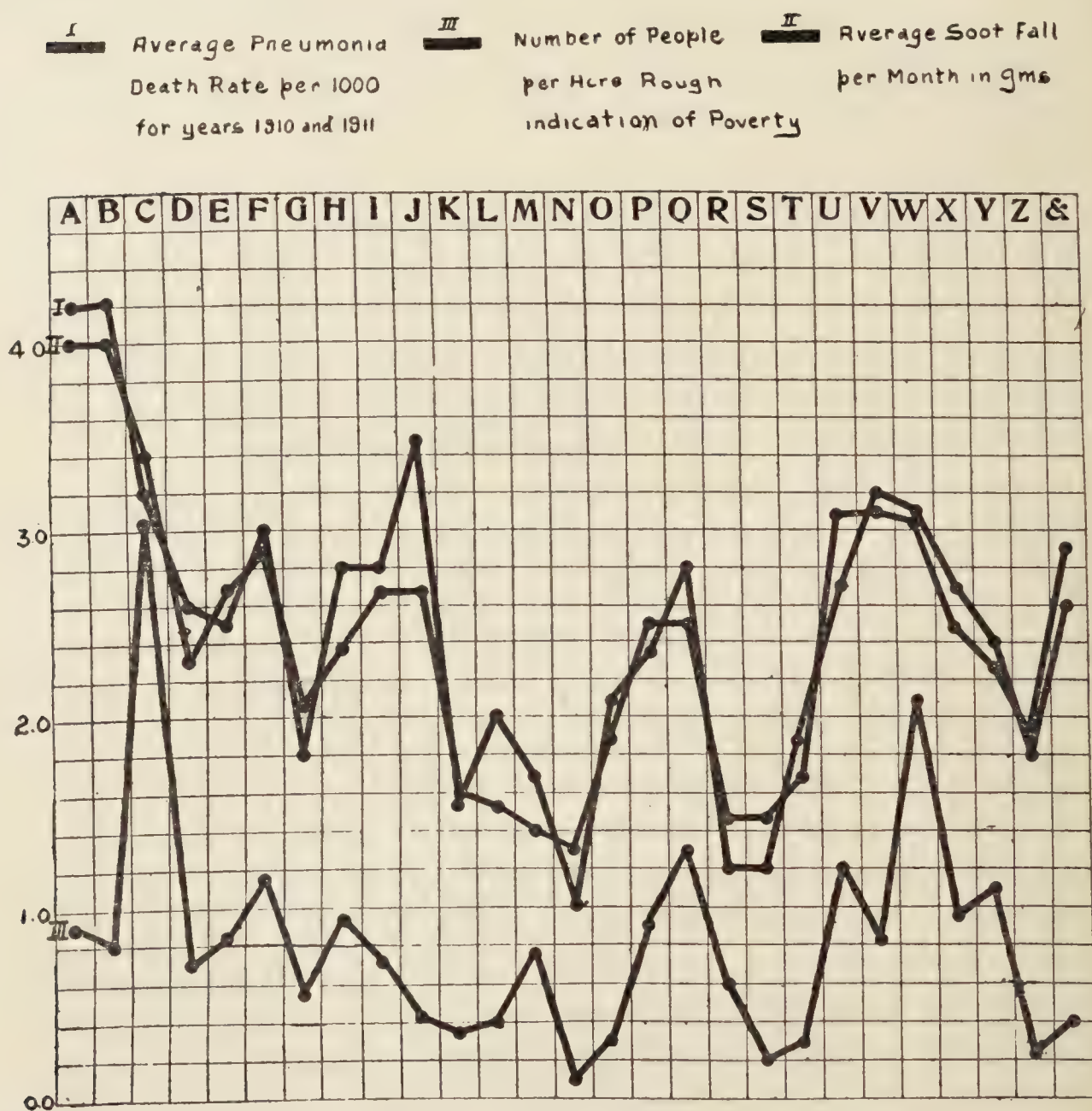
Chart III.

The mortality tables for pneumonia, on which Chart 4 is based, were secured from the Bureau of Census statistics.

We desire to acknowledge here the courtesy and kindness of Director Durand, of the Government Department of Commerce and Labor, for the prompt return of the smoke studies and statistical tables from the various cities, which we scarcely could have obtained without his aid.

Since 1905, Ascher, of Konigsberg, has published tables and studies on the relation of smoke to pneumonia and tuberculosis. Ascher's main conclusions are as follows:

1. The deaths from acute lung diseases are most frequent in children and old people. There is, from year to year, a steady increase in the number of these deaths. This is explained, in part, by the increased contamination of the air by smoke, because the increase in the number of deaths is greatest in districts of an industrial character and not in farming districts. Since 1875 the deaths of infants from pneumonia have increased 600 per cent.

2. There is a noticeable difference in the deaths of acute lung diseases, in those industrial districts where smoke contamination is greater than in those industrial districts where the smoke contamination is less. The number of deaths in coal workers from acute lung diseases is 130 per cent higher than the number of deaths in other workmen from the same cause and of the same age. Hand in hand with the increase of acute lung diseases there is a decrease in the age at death from tuberculosis. This means that the fatal course of tuberculosis in smoky districts is shorter.

3. Animal experiments show that the inhaling of smoke increases the susceptibility of animals to infection by aspergillus. Pneumonia develops in animals which have inhaled smoke more easily than in the control animals.

Ascher's experimental work can scarcely be used as a comparison with the influence of the smoky atmosphere of cities, because he used the smoke or soot of burning petroleum, which forms an insignificant amount of the smoke content of cities and differs very materially from the main content of the smoke of city air.

So far as Ascher's statistical tables are concerned, there can be very little doubt that acute lung diseases are taking a different course to tuberculosis, and one of the most appalling things of modern civilization has been the sharp increase of the mortality rate from acute diseases of the respiratory tract coincident with industrial activity and the consequent irritation by smoke of the

respiratory tract, this being in sharp contrast to the diminution of the chronic diseases of the respiratory tract, as exemplified by tuberculosis.

The pneumonia death toll for 1900 for the United States was 105,971; for 1909, 122,400; and for 1910, 136,000; an increase of 10 per cent in one year.

The average death rate from tuberculosis per 100,000 for the 10-year period 1900-1909 was 183; in 1909 it was 160.8; and in 1910, 160.3. This shows a steady decrease.
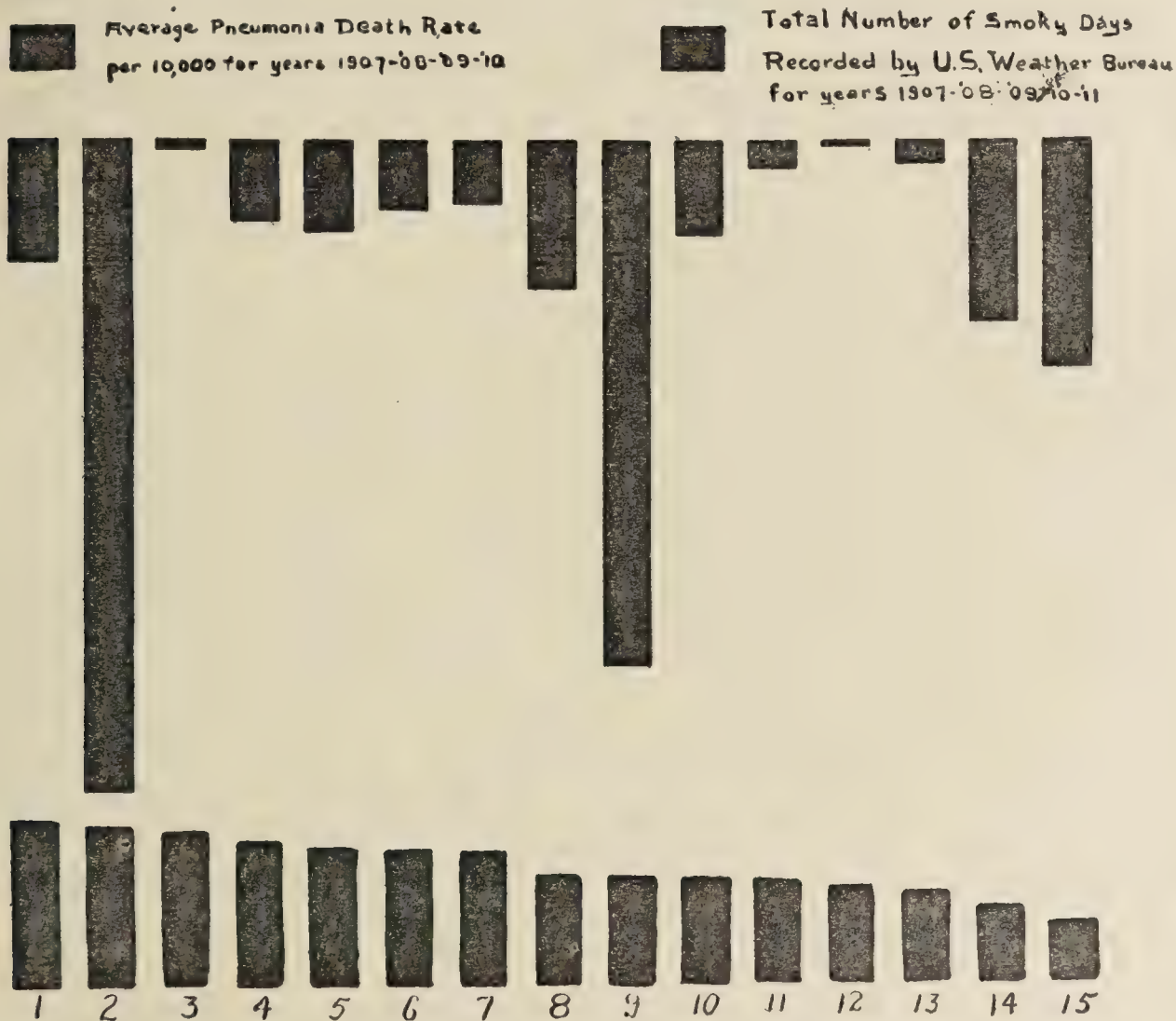
These figures are examples of the merit which this subject has for our most earnest study.

The chief fact which has stimulated our interest in the pneumonia problem in the city of Pittsburgh has been the terribly acute and fatal type of pneumonia which fills the wards of our hospitals. It can hardly be that this severity of infection has to do alone with the virulence of the germ; nor does it seem likely that it has to do with the generally low type of resistance which Pittsburghers have to this type of infection; rather, it seems more likely that there must be some factor present in Pittsburgh which does not operate in other cities. As we approached this subject we felt sure that we would be able to prove that this factor was the smoke of the iron and steel mills. How signally we have failed in this will be very evident from chart 4, in which is seen the striking contrast between Boston, with almost no smoke, and Pittsburgh, swamped with smoke, yet with approximately the same pneumonia death rate. The same sort of thing is apparent between Mobile, Ala., with almost no smoke, and St. Louis, Mo., with a very high smoke content in its air.

When we attempt to analyze the city of Pittsburgh on the basis of air content of smoke and pneumonia death rate, so striking is the correspondence between the pneumonia death rate and the smoke content of the air of the ward that we are convinced that smoke is a very important factor in the severity of the disease and that some other factor must operate in those cities where the smoke content of the air is not the determining factor in the

COMPARISON OF PNEUMONIA DEATH RATE AND SMOKE CONTENT OF FIFTEEN CITIES OF THE UNITED STATES.

Average Pneumonia Death Rate per 10,000 for years 1907-'08-'09-'10

Total Number of Smoky Days Recorded by U.S. Weather Bureau for years 1907-'08-'09-'10-'11

1·Chicago
2·Pittsburgh
3·Boston
4·New Orleans
5·Richmond Va

6·New York
7·Charlestown, SC
8·Cincinnati, O
9·St. Louis
10·Philadelphia

11·San Francisco,
12·Mobile, Ala
13·Cleveland.
14·St. Paul.
15·Portland, Ore.

Chart IV

pneumonia death rate. This correspondence is more striking even when we put in a line showing that there is no definite bearing of such other factors as poverty, race, and congestion. When, however, one turns to tuberculosis and analyzes the death rate from this disease by wards and charts it in comparison with the smoke content of the air, one finds that there is no association whatever. This corresponds with our clinical observations on between four and five thousand cases of tuberculosis in the last six years. As the result of this clinical study we have come to the conclusion that the general death rate from tuberculosis in Pittsburgh is low— that there is nothing in the smoke content of the air which in any way stimulates the onset of the tubercular process or militates against the rapidity of recovery from tuberculosis when once this disease has been contracted.

In other words, after having made an analytical study of the relation of smoke in the City of Pittsburgh, where it is possible, by virtue of its contour, to separate the atmosphere into "densely laden," "moderately laden," and "comparatively no smoke" areas, and in such a way as to rule out such influences as poverty race, and congestion, we are forced to the conclusion that the smoke content of the air has an apparently important bearing on the pneumonia death rate and comparatively little bearing on the tuberculosis death rate.

From the careful analytical studies of the character of the smoke in the city of Pittsburgh, carried out by Dr. Klotz and Dr. Holman in connection with this same work, there is added a purely chemical and physical reason for this same conclusion, for they have found that the percentage of phenol around the carbon, which pollutes the air, is sufficient to destroy most or many of the organisms with which they have studied when suspensions of these are mixed with suspensions of air smoke.

With this fact in mind it is probably legitimate for one to turn to the pathological studies of these two infections. Pneumonia is a catarrhal condition, and a pre-

disposition for it may be prepared by the irritation of the mucous membrances with foreign substances; but the second (tuberculosis), being granulomatous in type, in which the microorganisms are sequestered and surrounded by cells, the cure of which is accomplished by fibrosis, may naturally be supposed to be aided in the direction of cure by any deposit which stimulates granulation and fibrosis. Some strength is given to this theoretical view by the evidence which we have from anatomical studies, in which we find depositions of carbon particles around the healed tuberculous focus.

One can not help wondering why, when the facts concerning these two diseases are known, so little has been done on the question of pneumonia prevention, when so much has been accomplished on the tuberculosis side of pulmonary infection; and in addition to my remarks upon the relation of smoke to this disease, I should like to again call attention to certain suggestions which I offered a year ago in an address before the Ontario Medical Association for the control of a certain portion of the evils arising from pneumonia. These are as follows:

First. The proper segregation of pneumonia patients and their utensils in hospitals; cleaning, by sprays and washes, the noses and throats of all who nurse and come in contact with these patients; careful hand washing of nurses and attendants after handling; careful destruction of sputum and other discharges; sterilization of linen of patients; fumigation of rooms after occupancy; and the use of gauze, which can be burned, instead of handkerchiefs. These will be the center of the educational crusade.

Second. To have attached to our dispensaries certain nurses who have received special instruction on nursing and preventing the spread of pneumonia, these to be sent to all pneumonia cases in home-nursing work.

Third. The reporting of all such cases to the health department governing the district where the disease exists and the fumigation of the quarters in which the disease has occurred by the department after the death or recovery of the patient.

Fourth. The instruction of the public by pamphlets and school lectures on the necessity for keeping the noses and throats cleansed, especially during winter months; the necessity for controlling the dust of streets by better sprinkling and night sweeping; the evils of bad ventilation in house, public building, and school; of alcohol; of badly cooked poor food; of lack of rest; of worry; of the handkerchiefs; of the bearing on pneumonia of spitting, as well as on other diseases; of the increased resistance generated by open-air sleeping; and similar knowledge. This I am sure, can best be engrafted on the child's mind rather than on that of the adult.

The Influence of Smoke on Acute and Chronic Lung Infections*

WILLIAM CHARLES WHITE

AND

PAUL SHUEY.
Pittsburgh, Pa.

A year ago we started an investigation on the influence of smoke on the various problems of public health. We chose for our study the respiratory tract, as that in which smoke would have its greatest influence by direct contact.

The investigation was carried on under a grant given by Mr. R. B. Mellon to the University of Pittsburgh for the consideration of this problem from all its aspects.

At the International Congress of Hygiene and Demography we made a preliminary report of what had been accomplished up to that time, and while the work reported in the former paper was very incomplete, there seemed to be a rough direct ratio between the number of smoky days in any given city and the number of deaths occurring from pneumonia. On the other hand, there seemed to be an inverse ratio between the number of smoky days and the number of deaths from tuberculosis.

In choosing these two diseases, we were guided by the fact that the one (pneumonia) is an acute inflammatory process of short duration, likely to be influenced by acute irritation, such as would come from foreign particles, and that it represents the most striking malady from the standpoint of increased mortality in the greater number of our cities.

The other (tuberculosis) is a chronic infection, characterized by infiltration and healing by fibrosis, extending over a long period of months or years, and more likely to be stimulated to healing by irritation of inert foreign particles, and yet presenting a constantly decreasing mortality.

Following the presentation of the paper before the Congress of Hygiene and Demography, Dr. John S. Fulton, Secretary of the Congress, called our attention by letter to certain factors, which he felt were of more importance than the simple ratio of smoke to pneumonia mortality, and we have included these in the substance of our present study. The main points in Dr. Fulton's arguments against the conclusions which we tentatively drew from our study were as follow:—

"I would expect Boston to have a greater mortality from pneumonia than Pittsburgh, on the sole basis of fact that Boston has relatively more people in the pneumonia ages. I would expect Chicago to have a higher pneumonia mortality than Pittsburgh, because there is a pneumonia obsession in the minds of the medical profession of Chicago.

"Chicago has relatively more people in the pneumonia ages than Pittsburgh has, and relatively fewer in the pneumonia ages than Boston. I do not think that the pneumonia figures admit of sound reasoning as to magnitude, unless, in the first place, distinctions are made as to the age-distribution of the populations which are to be compared; and, in the second place, unless the pneumonia mortality is divided sharply into two groups, those under and those above the age of three years, and the comparisons made with reference to these distinctions.

"A comparison of pneumonia and tuberculosis magnitudes, as among the cities which you mention, does not prove that the prevalence of tuberculosis in Pittsburgh is low, or that the prevalence of pneumonia is high.

"By mere inspection of those pneumonia charts, without any key to the names of the cities concerned, I would

say that 1, 2, 3, 4, 5, 6 and 7 (Chicago, Pittsburgh, Boston, New Orleans, Richmond, New York and Charleston) are cities fifty years old or older. The last eight (Cincinnati, St. Louis, Philadelphia, San Francisco, Mobile, Cleveland, St. Paul and Portland) are cities less than fifty years of age, and probably situated west of the Alleghenies. I would be right with respect to the first group, and, with respect to the last group, my two errors would be Philadelphia and Mobile."

In choosing the cities for study, we have taken the larger cities scattered widely over the United States, and have tried to get as widely varying conditions from the standpoint of age of settlement, density of population, years of incorporation, flatness of contour as it was possible to obtain.

We have also analyzed more carefully the data on which we have completed our present study, and have ruled out as much as possible, in drawing our conclusions, the years and material which were unsafe to use by virtue of their lack of thoroughness.

In the charts accompanying the present study, in the smoke curve we have plotted the number of smoky days per year. In arranging the cities on the charts we have put the smokiest cities first, and so graded on down to the cities in which the smoke was the least. We have considered in arranging them in this way only the 1908 to 1912 periods, preferring to neglect 1907 on account of the unreliability of the mortality data of that year. It will thus be seen that Pittsburgh, St. Louis, Portland, St. Paul, Cincinnati, Chicago, Philadelphia, New Orleans and New York may be grouped as the smoky cities. In this group, however, Pittsburgh, St. Louis, Portland and St. Paul may be classed as very smoky cities.

Beneath these charts the figures represent:—

First (the top line), the number of years since the settlement of the city;

The second line, the number of years since the city was incorporated;

PNEUMONIA

TUBERCULOSIS

Smoky days per year

Deaths per 1000	Pittsburgh	St Louis	Portland,O	St Paul	Cincinnati	Chicago	Philadelphia	New York	New Orleans	Richmond	Cleveland	SanFrancisco	Indianapolis	Minneapolis	Memphis	Boston	Mobile	Los Angeles
Age of settlement	159	75	68	144	133	228	232	300	195	304	117	149	92	64	93	283	211	132
Incorporated age	97	59	62	63	94	76	212	260	108	131	77	91	82	53	64	91	99	62
People per acre	20.2	6.4	6.7	14.0	11.4	20.3	18.6	26.0	2.7	20.0	19.2	17.5	11.1	9.4	11.2	25.4	14.6	5.0
Smoky days	147.4	118.2	37.6	35.8	20.8	17.8	16.4	13.0	10.0	8.2	7.2	6.2	5.4	4.2	3.0	2.0	0.4	0.4

The third line, the density of population on the basis of the number of people per acre; and the

Fourth line, the average number of smoky days per year for the five-year period, 1908-1912.

In studying the death ratio of the different cities, we plotted the total death-rate and the death-rate of the white population, as well as the following groups:

Total population under 5 years.
  ”   ”   from 5 to 9 years.
  ”   ”   ”   10 ” 19 ”
  ”   ”   ”   20 ” 29 ”
  ”   ”   ”   30 ” 49 ”
  ”   ”   ”   50 ” 69 ”
  ”   ”   ”   70 years upwards.

While we plotted all these in the original chart from which this study was made, we have only included a few of them outside the total death-rate in the accompanying charts. In these curves, it is important to bear in mind the history of the registration area of the United States and the great variation in the thoroughness with which vital statistics are kept in the various cities. It was only in 1907 that the registration area approximated 50 per cent. of the population; and only in 1910 was any special attempt made at a uniform method of classification and registration, and this uniform method is not yet in operation in all of the municipalities which we have used. For instance, this classification is not in use in Philadelphia, nor in St. Lous.

In the various curves it will be observed that the year 1907 does not conform to the ratio which has been found to hold in years following this. This may safely be explained by the fact that 1908 was really the beginning of better attempts to place vital statistics upon a more uniform basis; and only in 1910-1911-1912 did we arrive at any real fair basis for comparison.

It must be borne in mind that in comparing with other cities, cities having a large coloured component of population, the mortality by age must be compared on a basis of the ratio of the mortality of the white population to the entire population, because the negro death-rates are much higher than the white.

It will be obvious immediately to anyone who attempts to study this field that the number of smoky days, as furnished by the United States Weather Bureau, is apt to be a very variable quantity, both from the personnel of the recorder and the method by which these readings are made.

The present method of determining the number of smoky days is by fixing the clearness with which certain established objects can be observed from the fixed point of the Observation Bureau. Such factors as the height of the Bureau from the ground, the acuteness of vision of the observer, probably the habits of the observer, the interest which the observer has in the problem, and similar circumstances make it almost impossible to lay down any fixed curve which will be comprehensive for all cities and it would seem a reasonable conclusion that if there is even a rough relation between the conditions which we are studying, it would be safer to say that with more careful figures a more intimate relation could be determined. For instance it is inconceivable that there should be no smoky days for 1910-1911-1912 in a city like Boston, which is largely a manufacturing centre. In the report of the District forecaster for Boston, there have only been two smoky periods in five years. These two periods were five days following September 1, 1908, and five days following October 15 in the same year, and were due to forest fires. While it seems almost incredible that in a manufacturing city, subject to fogs, there should not be more smoky days than is indicated by the forecaster's report, yet it will be noticed that in the Boston curve during this smoky period the pneumonia death- rate- decreased. It is a feature probably not of very serious import that during

that year the pneumonia death-rate fell in all pneumonia groups save that of 5 years of age. This evidence of the reverse influence of the number of smoky days per year on the mortality curve from pneumonia is apparent in several other cities, as for example, Cincinnati.

Between St. Paul and Minneapolis, lying very near together, there is also a marked discrepancy—St. Paul having in 1910 nearly 120 smoky days, and yet the reply from the Forecaster was as follows: "You are informed that said days with record of smoke had reference only to and not to local smoke due to factory chimneys, &c." It seems impossible that St. Paul should be affected with forest fires and Minneapolic not, with a few miles difference in position. This peculiarity of the smoke curve for St. Paul would, of course, put it out of place in this chart, and would explain the difficulty in tracing the same relation which is present in the other cities.

The same thing applies to Portland, from which we have not been able to receive an explanation of the large number of smoky days reported from that city. Portland is probably out of its place in this scheme, as its statistics are not complete.

In summing up these charts, which have been done as impartially as possible, the only constant factor which seems to have any relation is the smoke; in other words, where age of settlement, number of people per acre, and age of incorporation have any apparent influence, this influence must be coupled with the number of smoky days before any satisfactory conclusion can be drawn. It will be seen, then, that if we except Portland and St. Paul, there is a general tendency of the tuberculosis death-rate to rise as the number of smoky days in the city decreases. On the other hand, it will be seen that there is a general tendency for the number of deaths from pneumonia to fall as the number of smoky days in the city decreases. In this instance also, Portland, St. Paul and Boston must be excepted. There seems to be no definite relation, however, between the number of smoky days and the death-rate

under 5 years of age in the pneumonia group. This might readily be expected if we consider as the explanation of the influence of smoke on pneumonia the irritative changes which go on in the mucous membrane of the upper air passages as the underlying factor in this relation, and that these changes would probably take years in their production, or, as Dr. Haythorn has shown, the pneumonia difficulty may be largely one of absorption of exudate, which anthracosis by plugging the lymph spaces largely impedes.

In general, the tuberculosis age-groups are rather uniform in their relation to each other when one comes to the study of individual influences; probably nothing is more striking than the difference between the curve for the total death-rate of the white population as opposed to the coloured. This is most strikingly seen in such southern cities as Memphis, Mobile, New Orleans, and Richmond. There is a striking difference, also, in San Francisco and Los Angeles in the total death-rate from tuberculosis, due, likely, to importation from the middle-west and northern parts of the country.

When one studies individual cities, one finds, as in Pittsburgh, St. Louis, Cincinnati, Chicago, New Orleans, Richmond, &c., a noticeable similarity between the total pneumonia death-rate and the total number of smoky days. This is almost entirely absent in comparing the tuberculosis yearly death-rate, which has persistently dropped in most of the individual cities, save the southern ones, in which there have been curious rises. It is not our intention to enter into explanation of this feature in this paper.

We are at a loss to explain the high mortality rate from tuberculosis in Cincinnati, which seems to be out of its place in the general contour of this chart.

In Boston, in addition to the fact that we believe it out of place from the number of smoky days from a manufacturing standpoint, Dr. Fulton had suggested in his criticism of our former paper that the high pneumonia death-rate in Boston was probably due to the large num-

ber of people in the pneumonia ages (extremes of life). This our age grouping has not demonstrated, as the pneumonia death-rate in all ages is high in Boston. We believe that the factor which is absent in the compilation of this city is the number of smoky days in the year.

Chicago, on the other hand, where Dr. Fulton believes there is a pneumonia obsession in the minds of the physicians, follows very closely what one would expect from the readings of the smoky days. As nearly as we can find, Chicago has been very careful, and since 1910 has forwarded its certificates to Washington, where they have been classified by the Vital Statistics Division of the Census Bureau in order to obviate the reflection of local bias.

We believe that if it were possible to establish a reading of smoky days on the basis which Dr. Benner has established in Pittsburgh, i. e., the precipitation of soot, and have this uniform in the various cities, that we would be able to establish a much more intimate relation between the number of smoky days and the number of pneumonia deaths in any city.

One of the conspicuous things to us in Pittsburgh has been the virulency of the pneumonia infection, which, of course, varies from year to year, but seems to carry its toll off more quickly in Pittsburgh than in any other of the four cities in which I have lived and worked in this field.

It may be well here to again call your attention to the fact that pneumonia is in the main an increasing death-rate in many cities and in the country as a whole; that it takes its victims from the extremes of life; and also takes off many of our most useful middle-aged business men, i. e., many on whom most has been spent in education, at a time when they are most useful to the community; and if it were possible by municipal ordinance to control in some way the production of useless smoke in the cities, much might be done to conserve that on which the community has expended the most, and from which it

may reasonably expect returns in place of death by a rapid illness, such as the one with which we are dealing.

Source of Data.

The mortality statistics are based on reports received through the courtesy of Dr. C. L. Wilbur, Chief of the Division of Vital Statistics of the United States Census Bureau and also through the courtesy of the various Boards of Health of the different cities.

The population statistics and age-distribution for 1910 were obtained through the courtesy of Director E. Dana Durand, of the United States Census Bureau.

The smoke data we obtained through the courtesy of the Chief of the United States Weather Bureau.

Since the Census Bureau report for the year 1900 was as of the population on June 1 while the Census Bureau report for 1910 was as of population on April 15, we utilized the method used by the Census Bureau in estimating the population figures for intercensual years, and after determining the rate of increase, we reduced the estimates of populations to a uniform mid-year basis, *i. e.*, we have them to relate to July 1, with the exception of San Francisco, in which our mortality figures were for the fiscal year. For this city we took the population as of January 1.*

It was necessary to plot population curves to provide a comparison between the population statistics which are furnished on the basis of ten-year periods, starting with five as its unit digit after 35. The mortality statistics, on the other hand, are furnished on the basis of ten-year periods with zero as the unit digit above 30 years of age.

After the population statistics were plotted on this basis, computation was made from these curves for the age periods corresponding to the mortality statistics. The mortality rate per 10,000 was then computed and used in the building up of the curves of the other charts.

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* Bulletin 108, p. 9, and Bulletin 109, p. 9, United States Bureau of Census, Department of Commerce.

Publications of the Smoke Investigation

Bulletin No. 1.   Outline of the Smoke Investigation. 16 p.   Free.

Bulletin No. 2.   Bibliography of Smoke and Smoke Prevention.   164 p.   Fifty cents.

Bulletin No. 3.   Psychological Aspects of the Problem of Atmospheric Smoke Pollution.   46 p.   Twenty-five cents.

Bulletin No. 4.   The Economic Cost of the Smoke Nuisance to Pittsburgh.   46 p.   Twenty-five cents.

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Bulletin No. 9.   Papers on the Influence of Smoke on Health.   173 p.   Fifty cents.

ADDRESS OF DR. WILLIAM H. WELCH.

Delivered on the occasion of the presenta-
tion of the Ernst Ziegler Library to the
Medical Department of the University of
Pittsburgh by Mr. Richard B. Mellon, Dec.
5, 1913, at the University Club of Pitts-
burg.

Mr. Chairman, Ladies and Gentlemen:

Have you noticed in that all too
generous introduction that Dr. Arbuthnot
has given me he omitted one qualification,
that of a speaker, an orator? That is
precisely the qualification most needed on
this occasion, and I hope you will bear
with me for the manifest lack of it, which
is emphasized by its omission by Dr.Arbuthnot.
I do indeed deem it a privilege to come
here and share with the Medical Department
of the University of Pittsburgh their
pleasure in receiving this interesting and
valuable gift of books, and I rejoice that
I can bring congratulations to my friend
and colleague, Dr. Klotz, the Professor of
Pathology in this school. I do not know any
young pathologist today who is doing better
work and who is more deserving of the good
fortune which has come to him by having
this most valuable instrument of research,
for such indeed is the libary placed at
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education in the country; because, what
is for the benefit of one is for the
benefit of all. Therefore, it is indeed
with great satisfaction that I felicitate
this school and thank Mr. Mellon for his
generous donation.

I was not aware when I came here
precisely the character of audience that
I was expected to address. I supposed
it was to be made up mostly of physicians,
and my intention had been to utilize this
opportunity mainly for presenting some-
thing suggested by the collection of books,
particularly what these books signify and
all that the development of pathological
anatomy has meant for the science and art
of medicine. I cannot forego at least
touching upon those topics, although I
recognize that any adequate presentation
of them would be rather too technical and
hardly fitting for the occasion.

It is, of course, appropriate that a
few words should be said - (they have
already been well said)- concerning the
one who collected this library,- a
collection of books which received added
interest from the one whose thought is
embodied in the collection. Who was this
Ernst Ziegler? What did he mean for
modern pathology? He was for a quarter
of a century one of the most prominent
figures in the pathological world. Born
in 1849, dying 1905, a native of Switzer-
land, belonging to that second generation
of pathologists who were not the immediate
pupils of the one we regard as the great
founder of modern pathology,- Rudolf

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3.

Virchow,- one of the great names in
science of all times, - he was not an
immediate pupil, but he was a pupil of
the pupils of Virchow. He belongs to and
was perhaps the leader of that second
generation of pathologists to which I
refer.

I did not know him at all well, but
I have had the good fortune to meet him
more than once. I recall the first
opportunity was as far back as 1877, when
he was a young prosector, as it is called,
in the University of Wurzburg. I was at
that time a student in Germany, and I
made a little journey around the different
universities. Coming to the University
of Wurzburg, the Professor of Pathology,
Rindfleisch, who was one of the teachers
of Ziegler, was away, and I recall so well
the attention and politeness which I
received,- being then only a student,-
from this young prosector. He had just
done an interesting piece of work,quite
original, possibly as original as anything
he did later. I don't know how familiar
it may be to the investigators, the use of
the glass slides for drawing tissues, not
outside the body but within the body. He
came to interesting conclusions, not
altogether since substantiated, but, by
the methods then available, probably the
best which he could have reached. He was
at that time a young prosector who from
Wurzburg went to Freiburg, first as an
Extraordinary Professor, and then went
from there to the University of Tubingen

Virchow,- one of the great names in
science of all times, - he was not an
immediate pupil, but he was a pupil of
the pupils of Virchow. He belongs to and
was perhaps the leader of that second
generation of pathologists to which I
refer.

I did not know him at all well, but
I have had the good fortune to meet him
more than once. I recall the first
opportunity was as far back as 1877, when
he was a young prosector, as it is called,
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as Professor Ordinarius, where his name
is chiefly identified.

In 1881, he published that text
book of pathological anatomy to which Dr.
Klotz has referred. That first addition
of the Ziegler text book at once met the
needs of students of medicine, but it was
not received favorably by the professors
and teachers of pathology in Germany, -
that is often the fate of text books. The
destiny of a text book is determined
after all mainly by the suffrage of the
students and not by the opinion of the
teacher.

I don't know that I would remark it
really for publication, but I do recall
the remark of my old teacher, Reckling-
hauser, in Strassburg, whom I happened
to see soon after the publication of the
Beitrage; he said, "Qute an interesting
way to learn pathology. We all are aware
Ziegler doesn't know anything about
pathology, but to write a book on it is
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(Laughter).

The book was received favorably by
students, and edition after edition was
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pathologist of the day, but he was the
author of the most successful text book on
pathology, - I have seen it stated, perhaps
the most successful and popular text book
ever written. I imagine that the life of
a text book is about the life of the author;
that is, if not one of the great special
books marking an era, not one of the books
opening up new vistas to great pioneers and
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quarter of a century has met the needs
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Ziegler, as has already been stated,
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Then he was likewise the founder and
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fur Allgemeine Pathologie,- a journal of
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I met him after that occasionally when
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Now this collection of books, of
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By way of definition, pathology, - at least, we pathologists so define it, is the science, as distinguished from the

practice, of medicine. The aim is that
sooner or later the practice of medicine
shall be based upon this science. The
science has considerably outstripped the
practice; that is, there is a larger body
of knowledge as to the nature and cause of
disease than can at present be applied
either in its prevention or in its cause.
There are aspects of the subject of the
science of medicine which, particularly of
late years, have been more or less
specialized and separated from pathology.
In a narrower and more restricted sense,
pathology is more a study of the structural
alterations produced by disease; that is,
the body as revealed to us usually at post
mortem examinations. It may also be during
a surgical operation as the anatomical
changes produced in the body of disease;
that is, pathological anatomy, although a
study of the alterations, of the symptoms
and the activities of the body resulting
from these morbid changes, also belongs to
pathology.

Now, it was the cultivation of
pathological anatomy which for many years
had the greatest influence in the develop-
ment of modern medicine. There could be
no science of pathological anatomy without
the opportunity to dissect the dead body,
and in antiquity such dissections of human
beings were not made. Hence, there was no
pathological anatomy in antiquity. There
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disease, but there was no anatomical basis
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were premonitions in the 14th and 15th
centuries, but the real rise was in the
16th century, and the great reformer was
Vesalius, whose great "De Fabrica Corporis
Humani,"- a wonderfully artistic work,
illustrated, some claim by Titian,- although
that is probably not the case; certainly it
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representations of skeletons standing in
all sorts of poses and so on. Andreas
Vesalius' great work was published in
1543, if I remember rightly,- about the
middle of the 16th century.

There appeared early in the beginning
of that century really the very first work
on morbid anatomy, a real treasure. I am
not surprised it is not in this collection.
It is one of the most difficult of books
to pick up. The title is rather interesting,
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From that time for nearly three hundred
years there were observations on the changes
produced by disease in the human body as
revealed by dissection of the body- changes
in the lungs, in the heart and the various
organs of the body.   But physicians had no
conception as to the aid which they would
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these alterations produced by disease in the
body.   That is, it was not a scientific
pathological advancement, it was practically
what the title signified,- the wonderful
things, the curious things, the bizarre
things, the monsters.   All sorts of
remarkable observations are recorded and
they are very numerous, but that was the
sort of interest which the physicians of
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about three hundred years.

Just in the year 1700 there appeared in
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But they were of this character that I
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You can trace out observations and the
medical world will wonder how in the world
you run down that obscure reference.
(Laughter). With Vesalius, with Bonetus,
with Foester, you can cover the centuries
from 1500 to 1800.

But pathological anatomy is a science,
and who is its founder? Not Vesalius,
not Bonetus, not Foester. It is an Italian
name Morgagni, who published his great work
entitled "De Sedibus et Moriborum Causis,
per Anatomen Indagatis,"-"The Seats and
Causes of Diseases as Revealed by Anatomy."
Now appears a new conception; that of
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ical investigation. It may be encouraging
to note that that publication, which we
rank as marking a great epoch in the
history of medicine, in 1761, was published
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is hardly fair to bring that up, however,
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known views of my former colleague,Dr.
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It is a fact that we cannot, for the most
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Their descriptions are of symptoms and of
groups of symptoms.   You cannot tell what
fever they are talking about. They are
fevers; but as to attempting to recognize
any particular fever,- is it typhoid fever,
is it typhus fever, is it malarial fever?-
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And you could not do it until you found what
the real seats of the diseases were. And
that was the work of Morgagni.

Now, soon after Morgagni, an English
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I might say of Matthew Baillie that
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cane. This charming little book, which is
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That refers to the famous gold headed cane
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rather interesting, and gives, at least,
some food for thought. Baillie was a very
productive man for twenty years; then his
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There appeared at the turn of the
century the work of Bichat on Membranes and
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organs are made up of different textures,
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Bright, by the application of the systematic
study of the alterations which appeared in
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covered really the nature of the disease
which bears his name,- Bright's Disease.

I might say here that names of diseases
are not given to the possessors of the
disease, but to the doctors who describe
them; though it only too often happens that
the doctor who describes them,- it is a
curious thing- does really later on acquire
the diseases. I have even heard a very
witty after-dinner speech by Dr. Williams,
who is a well-known and excellent speaker
in which he commented on that fact. You
can imagine how it can be elaborated. You,
for instance, think you have developed an
extraordinary and interesting train of
symptoms, and the chances are that when you
go to the physician he is going to be
greatly interested in them. However, he
finds it to be some common ailment. But if
by chance you do succeed in getting together
a previously undescribed and unheard of
group of symptoms, do you get any credit for
it or is it the physician who takes
advantage of the opportunity and perpetu-
ates his name on the basis of your mis-
fortune? (Laughter).

But pathological anatomy in that led
to the recognition of a whole group of
diseases familiar today. Before that
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the diseases.   I have even heard a very
witty after-dinner speech by Dr. Williams,
who is a well-known and excellent speaker
in which he commented on that fact.   You
can imagine how it can be elaborated. You,
for instance, think you have developed an
extraordinary and interesting train of
symptoms, and the chances are that when you
go to the physician he is going to be
greatly interested in them.   However, he
finds it to be some common ailment. But if
by chance you do succeed in getting together
a previously undescribed and unheard of
group of symptoms, do you get any credit for
it or is it the physician who takes
advantage of the opportunity and perpetu-
ates his name on the basis of your mis-
fortune? (Laughter).

But pathological anatomy in that led
to the recognition of a whole group of
diseases familiar today.   Before that
pleurisy was not distinguished from pneu-
monia.   It could not readily be distinguished
simply by a study of symptoms.   As I say, one

of the great events was the use of this
method for the separation of typhoid fever
from all other forms of fever, and it was
in France that this work was most
efficiently done. But the sceptre passed
from France, perhaps in the beginning of
the fourth decade, to Vienna, and there
began working the greatest pathological
anatomist, I venture to say, who ever lived.
That was Karl Rokitansky, who for over
forty years, used (I do not like the word)
but we doctors do use it) the material of
the great general hospital in Vienna,
Allgemeines Krankenhaus. He embodied his
results in this great work on pathological
anatomy. He was not the greatest
pathologist, because I have explained that
pathology is used not only in the restrict-
ed sense of pathological anatomy, but
Rokitansky is the greatest pathological
anatomist who ever lived; and his descriptions
are the classical ones.

After all, most in this audience are
asking, "What does this bear on the cure of
disease?" It had this effect on the cure
of diseases and the treatment of disease.
I brought about what is known as the
Nihilistic School in Medicine,- A great
reaction in the belief in drugs as beneficial
in the treatment of disease. They said,
"Behold these conditions of the liver, of
the kidney, of the stomach, of the lungs!
What do you imagine a drug can do for that?
Is it conceivable that your drugs can have
any effect upon these conditions?" That is

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revealed at the post mortem examinations of
the wrecks, the ravages, the final terrible
stages of disease, are not, however, the
slow gradual deveopment of a process; and
the time to intervene is, of course,during
the period of development, and the nearer to
the initial period of development,the greater
the chance is. I won't elaborate the point,
but that was the great fallacy in the extreme
Nihilistic period as to the efficacy of
treatment of disease by medicine which pre-
vailed for a while in the Vienna School.

Then about the middle of the century,
from 1847 on, came the greatest name in the
history of pathology and one of the greatest
names in the history of medicine, that of
Rudolf Virchow, a great man in every sense of
the word; not only great in medicine, but
great in other branches of science. I have
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we know anything about Virchow in medicine,
saying, "He belongs to us, he is a great
anthropologist." Really, I think most
physicians have very little knowledge of the
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tions to the science of anthropology.

Then he was an influential man in
polition in Germany, a Liberal, and he did
great things for the city of Berlin in the
way of improved sanitation. I might say, in
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in those cities; better water supply,
better drainage; right ideas as to all
matters relating to public health were de-
veloped very largely by these men,-
Pettincover in Munich and Virchow, even at
an earlier date in Berlin.

But why do I say Virchow is the greatest
name in pathology? Because he founded
pathology on a sure foundation. The old
writers conceived of disease as seated in
regions; they did not get beyond that;
diseases of the chest, diseases of the
abdomen, diseases of the head. Morgagni
traced it to the organs; it is disease of
the lung, of the liver, and so on. Bichat
went further; it may be diseases of a
particular structure, of a particular tissue.
But Virchow traced it to what we may deem
today its ultimate seat, the cells of the
body.   He is the founder of what is known
as cellular pathology; that is the unit of
life, its seat, and we have not to this
day been able to trace disease back further
than to these microscopic cells. That is
the fundamental principle on which the sub-
structure is built.   There can be no con-
tribution to scientific medicine greater
perhaps in its purely scientific aspect than
this one,- the tracing of disease to the
ultimate cells of the body.

We cannot think today in other terms
than in terms of cells. You could not find
any student of medicine,- if he knew any-
thing about the structure, we will say, of
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to the structure, which, in its main out-
lines, scattering if you like, was erected
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This is a translation of the famous
work entittled "Cellular Pathology." Now,
it cannot be said that these studies in
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The highest point of view, of course,
for the pathological study of disease is
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As regards the discovery of Koch
it would not have mattered so much in
this country, it would not have mattered
so much in Great Britain; but in Germany
for a country doctor to venture to make a
great discovery is unheard of.(Laughter).
And Koch was a doctor in a little village
when he made these important researches,
first in anthrax, then giving us methods
of studying diseases, which, when combined
with the pioneer work of Pasteur's opened
up entirely new points of view in medicine
and founded the science of bacteriology.
This is only a part of pathology, as it is
also of public medicine or hygiene.

These pathological anatomists never
quite reconciled themselves to Koch. His
work made a very great sensation. It was,
of course, of a sensational character, and
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I shall never forget an incident
when I was a student in Breslau, working
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always cherished that little incident.

Now, these discoveries in bacteriology
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Whenever you can penetrate to the roots of a matter; whenever you can get a real insight into the essence of a thing; whenever you get the real causes of things; then there is a chance of getting power over the object of study. And we have that power to-day over a certain group of diseases, and we have it only because we have this deeper insight into the nature of those diseases.

What has made this direction in medicine so interesting to the general public has been, of course, the possibilities of the application of these new discoveries. What makes the appeal of medicine today so strong to philanthropists is precisely because they can appreciate what already has been done and because they can entertain reasonable hopes of what may be expected from further development along these lines. It is, therefore, the furthering of medical research which today meets such a generous response from philanthropists.

The application of these discoveries has been much more to the prevention of disease than to the cure of disease. It is in our power to eradicate completely many of the important great scourges of mankind. There is no question that malaria can be completely eradicated. I do not say it would be easy, but it could be. Yellow fever, more readily, in my judgment, could be completely eradicated. We have it in our power, in other words, so far as these infectious diseases are concerned, to a very large extent, to prevent

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them. Important as have been the
additions to our methods of treatment,
they have not been commensurate with
the additions to our capacity to prevent
the diseases.

Now, the average man can, of course,
be somewhat stirred to a realization of
the importance of preventative medicine,
but he comes back sooner or later to the
inquiry. "Well, what benefit is all this
in the treatment of disease?" Your
interest in medicine is personal or
domestic; it is your own ailment, or the
ailments of your friends or members of
your family that you are concerned in,
and you want to know how the doctor can
cure a cold or your rheumatism, or your
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have done it a hundred years ago. The
answer, of course, is not very satis-
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this decade of preventative medicime.
It is because when dangers are removed
from your path you don't realize that
they ever existed; any more than you in
Pittsburgh have any apprehension of
Indians or wild animals which once existed
here. When a thin is out of your path,
it is out of your mind. Hence, these
triumphs in preventive medicine do not
make the same impression upon the popular
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curative medicine.   A distinguished
surgeon at the great surgical congress
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In the past is has been surgery, the
great rewards have been in surgery.   It
is really through such prevention as
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fection that these great triumphs have
been made.

But the next great triumphs, I
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medicine, and some of the doctors here,
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This possibility of preventing a
certain groyp of disease applied only to
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diseases of childhood and of early life-
small pox, typhoid fever and other
diseases of early life.   The result here
has been a considerable diminution of
infant mortality and a marked increase
in the expectation of life, as it is
called.

The average duration of life,
counting from the year of birth on, has
been increased in the last century some
twelve years or so and the mortality has
been greatly reduced.   But these blessings
come to us only for the first 45 or 50
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ago, or a hundred years ago, but after
that you are not more likely to become
70 or 80 than you were 75 years ago.
There are some here, I think, who would
welcome that discovery. There has been
no discovery, no insight into the
diseases of advancing life. When the
discovery comes, when we understand
better what are the underlying causes of
that group of diseases, we can apply
similar practical applications with
similar results and similar benefits to
mankind. It is along those lines that
I think there are indications that dis-
coveries will be made.

As I say, this development in
modern medicine in modern times makes a
very strong appear to philanthropy. It
is not very many years ago that medicine
appealed in vain; it was passed by in
our universities. Medical schools were
the stepchildren; they weren't real
parts of the university; they weren't
integral parts of the faculty. That
cannot be said today. The medical school
today sheds luster upon the university and
sometimes it is the most important and
most renowned department of the University.
Medical education makes an appear today
which it never did before for support.

But the roots of research are in
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tion and research independently and neglect
the education on which research and
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institutions, but they have not
justified themselves. Of course,
institutions like the Rockefeller
Institute and the Carnegie Institute
of Washingto have abundantly justified
themselves by their results, but I think
it could be pointed out that if they had
been founded a decade before they were
founded they never would have justified
themselves.

It is on account of these dis-
coveries and improvements in education
that these institutions are rendered
possible and attain the results which
they do attain.

But I plead for the better support
of educational institutions as really
nourishing the roots of research; that
if you neglect those the tree will not
flourish, the fruit will not be borne,
and while there is room for a limited
number of these independent institutions,
and they serve a proper purpose, the great
need is of more abundant support of our
Universities, including, of course, the
medical school.

I will not speak further. There
are points that I had intended to touch
upon. There is much that might be said;
it is a theme by itself, of course, as
to the value of libraries to the Univer-
sities and to our medical schools.

I am a lover of books. I think it
needs no elaborate argument to make clear
to you that a library is an indispensable
possession of a University or Medical

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institutions like the Rockefeller
Institute and the Carnegie Institute
of Washingto have abundantly justified
themselves by their results, but I think
it could be pointed out that if they had
been founded a decade before they were
founded they never would have justified
themselves.

It is on account of these dis-
coveries and improvements in education
that these institutions are rendered
possible and attain the results which
they do attain.

But I plead for the better support
of educational institutions as really
nourishing the roots of research; that
if you neglect those the tree will not
flourish, the fruit will not be borne,
and while there is room for a limited
number of these independent institutions,
and they serve a proper purpose, the great
need is of more abundant support of our
Universities, including, of course, the
medical school.

I will not speak further. There
are points that I had intended to touch
upon. There is much that might be said;
it is a theme by itself, of course, as
to the value of libraries to the Univer-
sities and to our medical schools.

I am a lover of books. I think it
needs no elaborate argument to make clear
to you that a library is an indispensable
possession of a University of Medical

School. It is indispensable merely as an instrument of research; I put it side by side with the laboratory as an instrument of research. The investigator must have it. He must have the current journals, he must have the monographs, he must have them now, he must have them when he wants them. He cannot wait until he has them sent on from the Library in Washington, a splendid library, the greatest medical library in the world. He must have it now.

The teacher must have it too. I think the teacher who merely retails what he finds himself and is not at all a contributor to knowledge is a poor teacher. The really stumulating, inspiring teacher is the one who commands his subject and adds something to his subject, at least stimulates contribution to the knowledge in his own field. The practitioner must have it. Someone has said, I am not sure whether it was Dr. Osler, that the study of patients without reading is sailing on an uncharted sea, although reading without patients is not going to sea at all, but there should be combined the study of the patient,- of your object of study, whatever it may be,- with reading.

Ignorance of the literature of your subject may cost you unnecessary labor. You are attacking themes that have already been worked upon, possibly have already been developed, and you spend an immense amount of time and energy and talk and money in doing

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something which has already been done,
possibly better done.

I won't belabor the point. I am
sure you appreciate it. I am sure that
you realize that a library is an indis-
pensable possession of the medical
school.

I would plead for a larger
interest in the historical method of
approach to our subjects. There is a
fascination in books; not only merely
for their contents, but for something
about the author it may be, or something
about the period, something occasionally
about the binding. In other words,
there is an opportunity for the
bibliophyle; some like to call them a
bibliomaniac. There is an opportunity
for them in medicine as well as in
general literature.

There are collections of works
that mark eras and they are called
Medical Classics. This is a very
attractive thing, rather expensive I
will admit, but you can now and then
pick up such things. We have our
classics, even American classics, in
medicine.

These various sides of the uses
of the library for the teacher, for
the investigator, for the cultivation
of a nice historical sense, are
difficult perhaps to cultivate it you
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on the history of medicine. I have never
known anybody who succeeded in interest-
ing students in the history of medicine.
We have accomplished this in a measure by
the establishment of what we call our
Historical Club. Doctor Osler interested
himself greatly in that, and it has been
a very useful club and I think it is one
of the most interesting things we have in
connection with our university.

I may say in conclusion that this
Medical Department of the University of
Pittsburgh desires, above all, to have a
library building and all that goes with it.
We have long considered that the library
is the heart, the central thought,of the
medical school: and I have been very much
interested, indeed impressed, since I have
been here in Pittsburgh today in finding
how much they have at heart such a con-
ception at this. I speak of it not in the
sense of any plea, but on account of the
interest of that conception, and I fully
sympathize with it;- that the library should
be the central thought, the heart of the
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GOITRE IN FOWL.[1]

BY

OSKAR KLOTZ, M. D.,

University of Pittsburgh,
Pittsburgh, Pa.

During the early part of last fall, I received from Dr. Chevalier Jackson of Pittsburgh, a hen about eleven months old, hatched (incubator) from eggs of a fancy (Orphington) stock. The fowl was referred to me on account of a tumorous mass at the base of the neck on the left side, hanging over the left pectorals. The mass was the size of a tangerine orange, freely movable under the skin, and permitting considerable displacement from the pectoral region upwards into the neck. The tumor was well below the clavicle. No definite point of attachment could be made out on superficial examination, and no other nodules were recognized. The bird appeared in good condition, and was unusually docile. The tumor gave rise to no pressure symptoms, and did not inhibit the animal in feeding.

The rather superficial position which the tumor occupied permitted an easy approach by operation. The mass was well encap-

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[1] From the Pathological Laboratories.

sulated, and readily enucleated from its surroundings. It was found, however, that its attachment to the vessels at the root of the neck was very intimate, and an abundant supply of thin walled vessels passed into the capsule, and entered the substance of the gland. A firm ligature was passed about the base of the mass, leaving some of the tumor tissue attached to the large vessels. The tumor was removed and the vessels to the stump were not interfered with. During the removal, the circulation of blood within the enlarged and thin walled vessels could be readily observed.

The specimen which had been removed from the left thoracic region just below the clavicle consisted of a spherical tumor weighing 55 grams. The tumor measured 5.5x4.5x4.25 cm., which on account of shrinkage after the vessels were severed was smaller than the original mass when in situ. It was well encapsulated and its lower pole was closely adherent to the large vessels projecting over the thoracic opening. Large vessels were seen to course over the tumor as well as to enter its substance. The tumor was of a brownish yellow color and appeared to be made up of many small cysts and yellow granular masses. When cut through, a thin yellowish secretion escaped. The cut surface

Fig. I. Colloid goitre of hen.
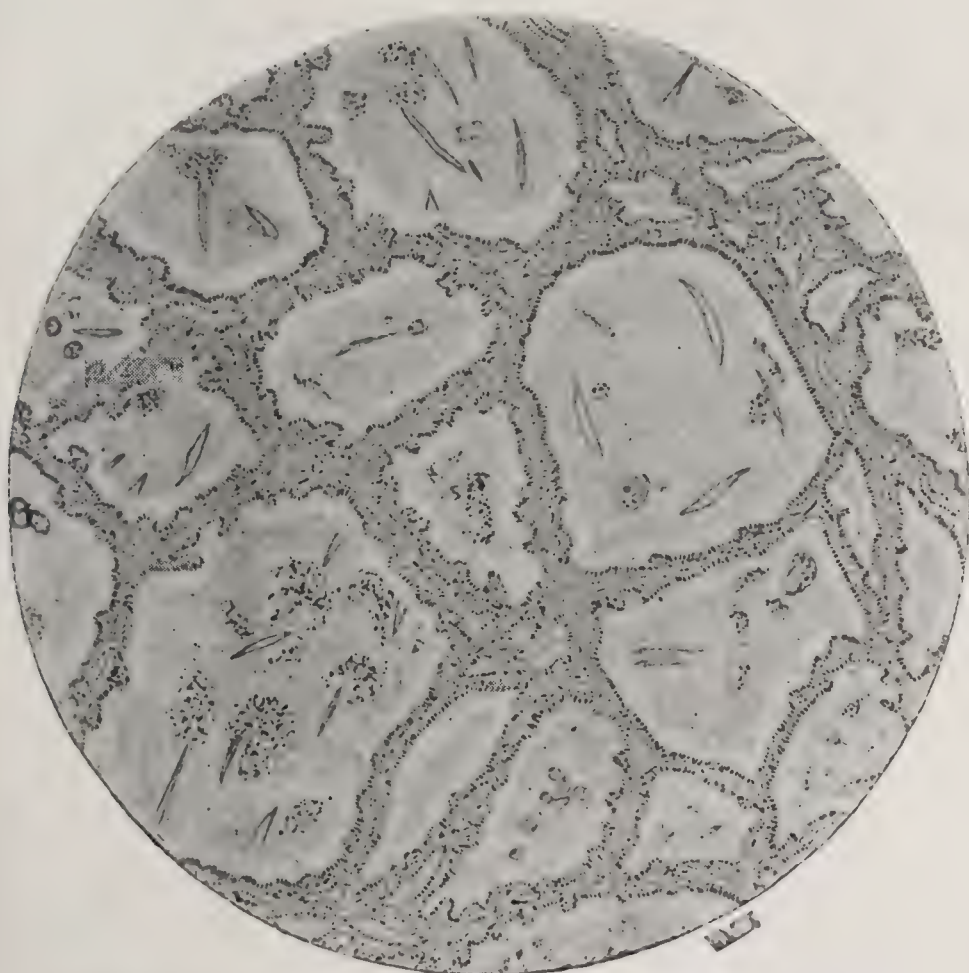
Fig. II. Colloid goitre of hen. Blood pigment
and cholesterin in colloid secretion.

showed a shiny and diffuse stroma between whose strands many small cystic cavities, some of which contained a glassy colloid material were found. Some of the cystic areas also contained small yellow, almost fatty looking masses. Much of the secretion was quite watery.

Sections of the tumor showed a loose alveolar arrangement with relatively little stroma. The alveoli formed large spaces containing a secretion, in part being like colloid but not infrequently showing the presence of many desquamated cells as well as leucocytes, These alveoli with open spaces were large and of relatively uniform size. They were lined by cubical cells which were quite regular. In some of the areas, the tissue was more solid and the alveoli were small and not dilated. The epithelial structures here tended to form gland-like masses with small lumina and only occasionally containing colloid. In these smaller epithelial structures the lining epithelium was thrown into folds and in part appeared as if there was some proliferative reaction. In the same field could be seen dilated alveoli with homogeneous or granular contents, and small hyperplastic alveoli with irregular epithelial lining. Here and there the contents of the alveoli showed the presence of clefts like those left by cholesterin crystals. Hemor-

rhage was not uncommonly observed within the alveolar spaces. In some instances this hemorrhage appeared quite recent and the blood cells were well preserved. Elsewhere again, blood pigment was present within large mononuclear cells and leucocytes which had migrated into the alveoli.

True goiterous tumors in fowl appear to be quite unusual. The normal thyroids in birds may be quite readily demonstrated in close connection with the great vessels at the root of the neck.

A further report of the clinical manifestations and of the chemical nature of the thyroid contents will be made by Dr. David Marine of Cleveland.
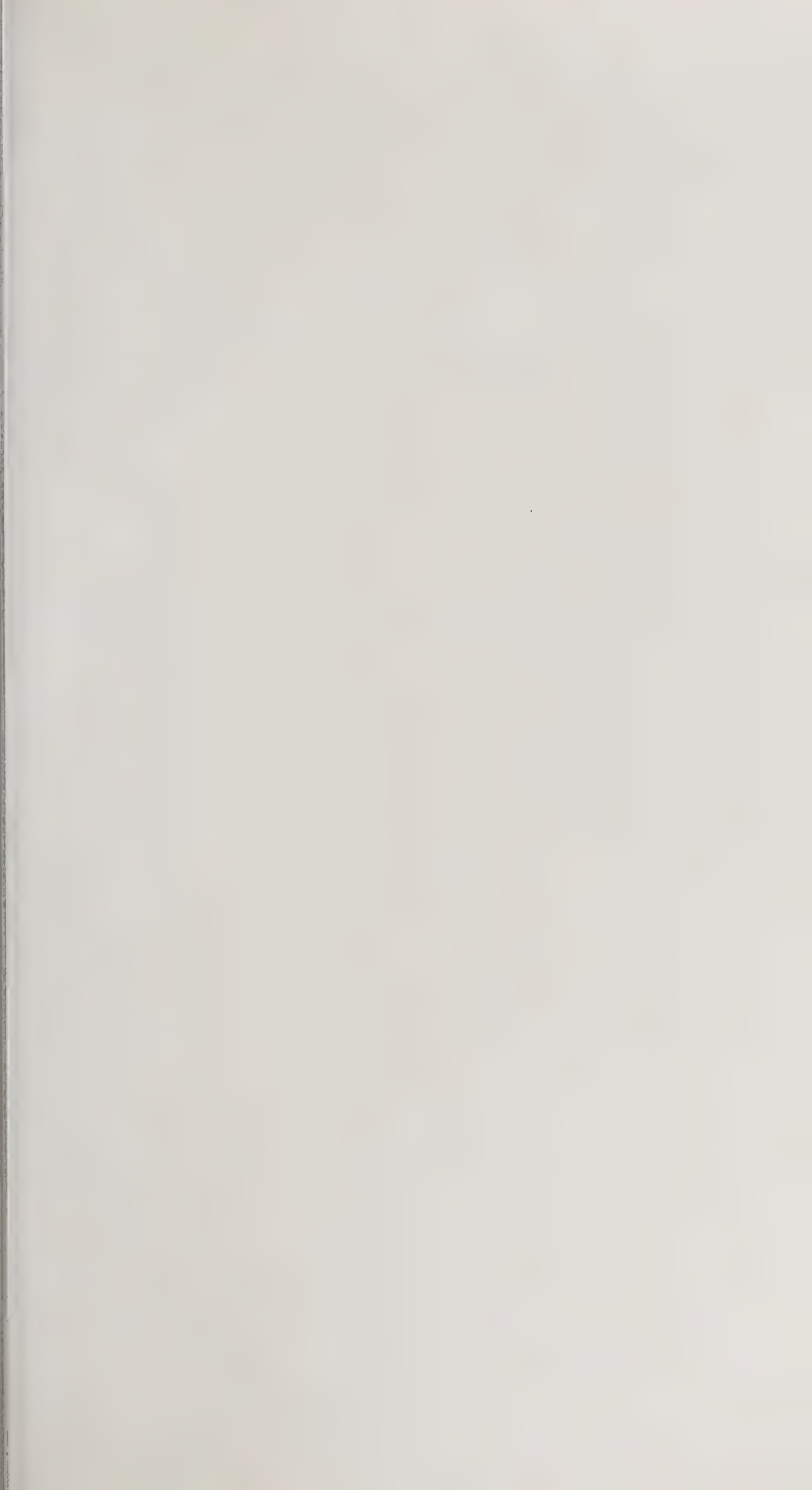
LIPO-AMYLOID DEGENERATION

OSKAR KLOTZ

(From the Pathological Laboratories, University of Pittsburgh,
Pittsburgh, Pa.)

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BOSTON
MASSACHUSETTS
U.S.A.

LIPO–AMYLOID DEGENERATION.[*]

Oskar Klotz.

(*From the Pathological Laboratories, University of Pittsburgh, Pittsburgh, Pa.*)

Amyloid, a homogeneous, semi-solid substance deposited as a product of altered metabolism has been demonstrated by Krawkow to be a compound of chondrotin sulphuric acid and a protein body. The protein base which was isolated had the characters of histon as isolated from the thymus. These observations were confirmed by Neuberg and others. It was, however, indicated that the most constant factor in the composition of amyloid was the chondrotin sulphuric acid while some variation occurred in characters of the protein base in various samples of amyloid studied. It is agreed that amyloid is not a true chemical entity, but that a variety of amyloid-like substances occur which may account for the variation in the microchemical reactions frequently reported (Schmidt). Nevertheless, it would appear from Raubitscheck that the amyloid materials from different sources are similar in the biological reactions as determined by the precipitin reaction after the inoculation into animals.

The chondrotin sulphuric acid radical entering into the composition of amyloid is a normal constituent of body tissues and may be demonstrated in cartilage, elastic tissues, particularly the aorta, tissues of the spleen, ligamentum nuchæ and the interstitial tissues of the glandular organs. The wide distribution of this substance may account for the deposition in so many tissues of the amyloid substance in general amyloidosis. It is suggested that the protein derivative under the circumstances of chronic bacterial infections as well as other processes of protein decomposition, becomes unusually available and by the interaction of a ferment the combination to form amyloid results. Definite knowledge of this process is not available.

What we are particularly interested in is the feature of amyloid being deposited extracellularly and giving rise to tissue disturbances mainly through mechanical interference. The continuous deposit of amyloid in the sub-endothelial tissues of the small blood vessels and capillaries or as in the kidney, its occurrence in the connective tissues around the tubules, brings about a disturbance of function of the part by direct pressure or by an interference with metabolism of neighboring cells. Pressure effects upon the liver cells are readily demonstrated. The amyloid process gradually encroaches more and more upon the area occupied by the liver cells until pressure atrophy leads to their disappearance. It is quite remarkable that as these parenchymatous cells become surrounded and shut off from the neighboring vascular channels their atrophy is not associated with much change other than the accumulation of small quantities of fatty granules within the cells. Necroses are not observed.

In studying the accumulation of amyloid in the liver and kidney some interesting observations on the occurrence of fat in the involved areas were made. In the regions of early amyloid deposit, fat or lipoid bodies are not to be demonstrated either in the amyloid deposit or in the liver cells. As the amyloid increases in quantity a granular lipoid substance accumulates in the neighboring liver columns. This fatty material stains with sudan, has a blue reaction with nile blue sulphate, does not show double refraction with Nichol's prism and is less soluble in alcohol than the fat globules of healthy liver cells.

As the amyloid material increases in the sub-endothelial spaces a fat staining material appears in the deposit. This fatty material is more or less diffused through the deposit, being more intense in its central portion than in the periphery. These lipoid substances may be demonstrated in the stained amyloid deposit by sudan, and stain blue with nile blue sulphate. They show no evidence of double refraction and appear incorporated within the amyloid, showing no globules or apparent granules. By Ciaccio's method no sudan staining masses were observed. In the presence of the lipoid

material the amyloid still retained its specific staining quality. We have found, moreover, that the fatty material may readily be removed by fat solvents without altering the amyloid reaction. It would thus appear that the presence of the fatty material is in physical rather than chemical combination with the amyloid deposit.

The amount of fatty materials is in proportion to the extent of the amyloid deposit, and it is found that the fat accumulates in the center of the areas, forming wormy masses with no apparent relation to the configuration of the original tissue. The appearance of the masses suggests a partial saturation of the amyloid substance by a lipoid suspension.

The accumulation of lipoid bodies within amyloid areas is seen not only in the liver but also in the arteries, spleen, glomerular tufts, and extratubular accumulations of the kidney. Although, as has been previously indicated, the neighboring tissues of the amyloid deposit suffer degenerations of different kinds including the fatty, lipoid bodies do not ordinarily appear within the amyloid material. It would seem at first sight that the presence of the fat staining substances occurred subsequent to the destruction of some of the fat-containing cells in the vicinity, permitting their fat content to mingle with the amyloid. This would appear to explain the presence of the amyloid fat deposits of the liver. On the other hand, many of the smaller arteries showing amyloid, as well as the intertubular deposits in the kidney, are not necessarily accompanied by fatty degeneration or destruction of the neighboring cells permitting the mechanical escape of fat in their vicinity. Particularly is this true of the capillaries and arterioles of the heart where a lipo-amyloid deposit is sometimes present in the arterial wall without demonstrable fatty degeneration of the surrounding tissues. It would appear that in part, at least, some of the fat appearing in areas of amyloid deposit has been deposited from the tissue fluids, while in other instances the fat is derived by its liberation from degenerating cells.

The accumulation of lipoid bodies in the areas of amyloid degeneration has also a significance for the observations on

the deposit of fat in arteries subject to hyaline degenera-
tion, as well as on the presence of the so-called fatty degen-
eration of the elastic fibers. The development of much
hyaline in the thickened intima is a common observation in
chronic endarteritis, while the subsequent accumulation of
fat in these same areas is not unusual. Besides the fatty
granules which make their appearance in the tissue cells of
these areas a considerable amount of lipoid substance
appears extracellularly and in a diffuse infiltration. Com-
parable observations are made upon degenerating elastic
fibers which, when they are losing their specific staining
characters, become impregnated by a fat-staining substance.
It is probable that the conditions favoring the deposit of
lipoid bodies in these somewhat similar inert substances are
comparable.

NODULAR ENDARTERITIS OF THE AORTA ABOUT THE INTERCOSTAL ARTERIES

OSKAR KLOTZ

(From the Pathological Laboratories, University of Pittsburgh, Pittsburgh, Pa.)

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NODULAR ENDARTERITIS OF THE AORTA ABOUT THE INTERCOSTAL ARTERIES.*

OSKAR KLOTZ.

(*From the Pathological Laboratories, University of Pittsburgh, Pittsburgh, Pa.*)

Endarteritis is one of the most prominent and widespread reactions of the arterial tree. It is found in arteries of all sizes, and it is mainly through it that circulatory disturbances (referable to arterial disease) in different viscera are brought about. The variety of types of this disease have been repeatedly indicated (Virchow, Thoma, Friedemann, Jores, Chiari, Buerger), and although the disease process has been classified according to its gross character (diffuse, nodular, obliterating, thrombosing), this classification only takes cognizance of the fully developed lesion, when such changes as may readily be observed by the naked eye are recognized.

In endarteritis we must recognize a reaction which is very commonly seen on the intimal surface of the arteries, under most varied conditions. Not only have types of endarteritis been found associated with different systemic diseases (nephritis, Friedemann; lues, Heubner; acute infections, Simnitsky), but it is a very frequent accompaniment of a variety of other reactions in the arteries themselves. In known inflammatory processes of the arterial wall, particularly in syphilis, as well as in periarterial tuberculosis, an endarteritis is the rule, while an endarteritic process overlying an area of fatty degeneration in the deep intima is also common. On the other hand, small plaques of chronic endarteritis may appear in a vessel without evidence of a periarterial or medial inflammation and in the absence of any processes of degeneration in the deep intima which could be suggested as the causative factor in stimulating the overgrowth of the superficial layers. Recognizing, therefore, that the overgrowth of the superficial intimal tissues may be a response to irritants of different kinds, it was determined to study a series of vessels in the

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earliest stages of the process, as well as to collect observations upon the possible presence of reaction in a variety of infectious diseases, where naked eye lesions were not to be found. For the latter, studies were particularly carried out upon arteries of young individuals (ten to eighteen) who had just died of an acute infection (pneumonia, infective endocarditis, peritonitis, typhoid fever). The tissue for study which was selected was the aorta in the vicinity of the intercostal arteries. Moreover, similar studies were made upon individuals of more advanced years (thirty to sixty) who likewise had died of an acute infection. Here it was desired to observe the reaction, if any, which developed in or upon preëxisting nodular areas of the intima.

The presence of button-like areas of chronic endarteritis about the mouths of the intercostal arteries has been commented upon frequently. Similar isolated areas of endarteritis are observed about the mouths of other vessels branching from the aorta, but in frequency of distribution the descending thoracic aorta shows the nodular endarteritic thickening more commonly than the remaining portions of the central vessels. Their position upon the posterior wall and particularly about the intercostal arteries is characteristic, but difficult of explanation. For the distribution, particularly when it is recognized that their position is along the best supported portion of the aorta, the mechanical theory alone is wholly inadequate. That the intimal reaction is not in reponse to a medial weakening we hope to demonstrate in the subsequent discussion. And further, that we are not dealing with a process of response to simple " wear and tear " will, we believe, also be evident from this study.

We wish it to be clearly understood that the study here detailed deals with cases of infection and the cases have been selected on that account. We do not wish to have our conclusions misinterpreted as meaning to indicate that all processes of endarteritis have this origin, but rather to demonstrate that endarteritis may have an infectious origin, in which an inflammatory reaction, having a course not unlike that in other tissues and accompanied by fatty and

other degeneration, may be observed. Here again it may be well to indicate that the mode of origin or the previous course of a fully developed plaque of endarteritis cannot be determined by a study of the old lesions alone, and it is futile to hold controversy over such an indeterminable problem. A study of the earliest stages of the lesions in the tissues of man is still the most secure upon which to base conclusions. Animal experiments in our own hands have given inconstant results, though an endarteritis has been produced in very young rabbits by the inoculation of B. typhosus, streptococci, and staphylococci (Crog, Klotz, Saltykow). Hence when in young individuals, tissue reactions in the arteries may be demonstrated in association with a definite systemic disease and infection, and the ear-marks of these reactions are comparable to the known reactions of these bacteria in other tissues, we are justified in indicating a direct or indirect relation between the vascular lesions and the systemic disease.

Whether the lesions discussed in this paper are to be spoken of as arteriosclerosis may not find universal agreement, and is dependent upon the interpretation by the many observers of the nature of the arteriosclerotic process. For my own part (as well as Marchand, Faber and others) the term arteriosclerosis is generic, not defining any one particular disease, but a process induced by a variety of factors whose end-result is a hardening of the arteries. I would, however, point out that although inflammatory reactions induced by bacterial irritants are, for the most part, of a productive (so-called regenerative) kind, they are commonly accompanied by degenerative processes. Fatty degeneration is prone to follow the various chronic productive lesions of the intima, where, by the very nature of the normal structure, a disturbance by thickening of its surface layer leads to nutritional depression. In luetic arterial lesions this degenerative reaction, even though the intima is much thickened, is often lacking, as the nutritional disturbance by the thickening of the inner coat is compensated by the extensive development of new vessels from the vasa vasorum.

It is to be remembered also that degenerative changes of
the intima develop not only as a result of nutritional distur-
bances, but also through the action of noxious agents directly
upon tissues and cells. It has been amply demonstrated that
a variety of tissues and cells of the intima become involved in
fatty degeneration, the sum total of which make up the areas
of atheroma visible to the naked eye.

The materials studied comprised a series of twenty cases,
ranging in age from ten to fifty-six years. The cases were
selected with particular reference to the presence of a sys-
temic infectious disease. In many of these bacteria were
demonstrated during life by blood culture or at autopsy from
the heart, peritoneum or lung. Control observations were
made upon tissues obtained from a number of non-infectious
cases.

Case.	Sex and Age.	Cause of Death.	Infection.
1	M. 10	Scarlet fever and otitis media.	
2	M. 11	Scarlet fever and suppurative angina.	
3	F. 13	Acute verrucose M. endocarditis (chorea).	Strept. salivarius.
4	F. 13	Appendicitis.	
5	F. 15	Acute verrucose M. and A. endocarditis.	Strept. fecalis.
6	M. 17	Acute verrucose M. endocarditis.	Strept. salivarius.
7	F. 18	Acute lobar pneumonia.	Pneumococcus.
8	M. 20	Appendicitis.	
9	F. 23	Typhoid fever and peritonitis.	B. typhosus; strept. pyog.; B. coli.
10	M. 25	Typhoid fever.	B. typhosus.
11	M. 26	Recurrent M. and A. endocarditis.	Strept. mitis.
12	M. 28	Typhoid fever.	B. typhosus.
13	M. 29	Appendicitis.	
14	M. 30	Acute lobar pneumonia.	Pneumococcus.
15	F. 33	Typhoid fever.	B. typhosus.
16	M. 34	Acute lobar pneumonia.	Pneumococcus.
17	M. 39	Acute dysentery with peritonitis.	B. dysenteriæ (Flexner varians); B. coli.
18	F. 48	Acute lobar pneumonia.	
19	M. 55	" " "	Pneumococcus.
20	M. 56	Strangulated hernia and peritonitis.	Strept. pyog.; B. coli; Staph. aureus.

Sections were cut of the aorta in the neighborhood of the intercostal vessels. These sections were made by cutting the blocks (paraffin) in different planes, transverse, longitudinal, and on the flat. An opportunity is thus given to study the disposition and grouping of cells, which cannot be

obtained by a study of one set alone. Particularly valuable were the sections cut and mounted serially, which were obtained by cutting on the flat, beginning with the intima and ending in the adventitia. These blocks were taken so as to leave an intercostal artery in the center. By observing the tissues about the mouths of the intercostal vessels, and following the reactions in the vessel as it passed through the aorta, a good picture could be gained to indicate the nature of the process which terminates in nodular endarteritis. These sections made from flat portions of the aorta demonstrate an entirely new character to the deposition of the elements in the arterial wall. The arrangement of the cells in each succeeding layer is well brought out, while any alteration from the normal character or the presence of foreign cell elements is the more striking and quickly recognized.

The alternate sections of the paraffin blocks of each series were stained with hematoxylin and eosin, and by Verhoeff's method for elastic tissues. At the same time frozen sections were also made from adjoining areas of the vessel wall and stained with Sudan III. and hematoxylin, and a double stain of Sudan III. and Verhoeff's. The frozen sections of the aorta on the flat, stained by Sudan and hematoxylin were unusually instructive. The disposition of and the elements involved in the process of fatty degeneration were readily recognized.

The intercostal arteries are not individual and self-contained structures until the outer border of the aorta is reached. At their mouths on the inner surface of the aorta their boundary consists only of the intima of the aorta which dips downward and continues as the intimal lining of the efferent vessel. The internal elastic lamina of the aorta is also continuous with the innermost elastic layer of the intercostal vessel. Other than this, a thin intimal structure with an outer elastic zone, the intercostal artery possesses no elements of its own during its passage through the inner two-thirds of the aorta. In the outer part of the aorta the perforating artery gradually takes form, and elements from

the wall of the aorta enter into an orderly arrangement imitating a small vessel of the elastic type. The internal elastic lamina becomes more marked, and the media is well supplied with concentrically arranged elastic fibers. Moreover, in the outer part of the aorta, and while still within the media, the perforating intercostal vessel shows a fibrous tissue adventitia in which lymphatics and small blood vessels may be demonstrated. Thus the point of exit of each intercostal artery has a fibrous tissue mass which continues to surround the artery in the outer third of the aortic media. This connective tissue invasion of the aorta simulates that seen about the vasa vasorum, with this difference that the intercostals as they pass through the outer part of the aorta are provided with their own vasa vasorum.

The elastic elements entering into the structure of the efferent vessel vary in their arrangement from the inner surface of the aorta until the artery emerges from the adventitia. The elastic elements of the deep layer of the aorta are continued into the intercostal branches forming a definite boundary separating the elements of the media of the aorta from the intimal tissues of the branches. At times, this inner elastic boundary is sharp and definite, forming an elastic ring as is found in the peripheral arteries. At other times again the inner elastic lamina is an ill-defined layer which does not differ from the elastic elements which surround it on the outer side, and which are essential elements of the media of the aorta. It is observed, however, that as the branching artery passes through the aortic wall the elastic bands take a more definite arrangement to the efferent artery, and become disassociated from the elastic fibers in the media of the aorta. Moreover, in the outer part of the aorta the perforating vessel possesses a definite internal elastic lamina of its own simulating more the arrangement of this tissue in the peripheral vessels.

During the passage of the intercostal arteries through the wall of the aorta they do not possess a true media. The tissues which support the small artery belong to the aorta. The muscle and elastic elements of the media separate at

different angles leaving an oval opening but which, on account
of the many directions of the spaces, form a central circular
lumen. From these neighboring tissues a number of fibers
are given off which enter into the composition of a more or
less circular structure, the intimate wall of the efferent
artery. In the outer third of the aorta this arrangement
becomes more and more a part of the new vessel, until at the
point of exit the artery possesses its regular layers. The
character of the new vessel is that of the arteries of the
elastic type where the media is richly supplied with elastic
fibers. However, these elastic elements do not maintain a
parallel arrangement to each other as do those in the media
of the aorta. At a little distance from the aorta the elastic
fibers gradually diminish in number until the media contains
only sparse and branched elements as are present in other
peripheral arteries.

In a like manner the muscle cells within the wall of the
branching artery are but elements derived from the parent
vessel. Their course lies parallel with the elastic fibers,
some simply diverging from their usual direction to permit
the efferent vessel to pass, others taking a somewhat circular
course about the perforating lumen. Muscle cells were not
noted in connection with the deep layer of the intima.

The intima of the intercostal branches as they lie in the
wall of the aorta appeared very simple. An inner endothe-
lial layer lies upon a narrow strip of connective tissue. No
other elements than fibrous tissue were observed in this sub-
endothelial coat. The indefinite inner elastic lamina marked
the outer bounding of the intima and separated it from the
tissues of the media of the aorta. As noted before a true
media distinguishable from the tissues of the media of the
aorta does not exist for these efferent arteries during their
course through the wall of the aorta.

Recently Yamagiwa and Ito have shown that the mouths
of the intercostal arteries are each provided with a valve-like
lip which projects downwards from the upper border. Such
a projection would tend to develop unusual currents about
the openings of these vessels and possibly lead to small

whirlpools under the projecting margin. It is claimed that some of these thickened borders contain muscle bundles. We have been unable to demonstrate them.

Thus the exit of the intercostal, as well as the small intervertebral arteries, differs materially in its architecture from that of the large vessels of the arch. The character of the opening on the surface of the aorta, no doubt, gives rise to a different blood current than at the mouths of the larger vessels where a more or less steady stream constantly rushes through. To measure and examine the character of these currents is not possible, and a mathematical determination, dependent upon the size of the lumen of the vessel, is not justified by fact. It is not probable that the different character of the blood stream over the surface of the arteries is alone sufficient to stimulate histological changes in the intima, but it may have a bearing upon the localization of bacteria or the influence of their toxins upon the underlying tissues.

The character of the reactions observed in the walls of the arteries of the cases studied showed a considerable variation. Most instructive were the vessels of the younger individuals where no evidence of a previous reaction or disease was present. In the arteries of older individuals care must be exercised in separating the tissue changes which may be of recent date from those of longer standing and different causes. Attention must, moreover, be paid to all portions of the arterial wall, noting the reactions in the adventitia and media as well as the intima. As we have previously pointed out, an inflammatory infiltration is not uncommonly present about the vasa vasorum, and in our study upon the arterial lesions of acute rheumatic fever particular stress was laid upon this, because of the possible sequelæ of acute destructive mesarteritis or of chronic interstitial mesarteritis. In our former study the slight lesions observed in the intima were not further studied, it being indicated, however, that some reaction of infiltration by wandering cells and proliferation of the connective tissues was evident.

In our present observations the consecutive changes have

been followed, to indicate the process whereby the mild and early change in the intima gradually assumes the characters so commonly described as chronic endarteritis. In whatever manner the active factor of the systemic disease may act, whether by the bacteria, their toxins or through disturbed metabolism, will not at present be further discussed. We can only indicate that an irritant is present, whose response is a tissue reaction, infiltrative, proliferative, and degenerative.

The earliest response we have observed in the intima is a loosening of the narrow connective layer, simulating an edema. The change may be very slight, but sufficient, nevertheless, to show that the thickness of the tissues on the inner side of the internal elastic lamina (of both central and peripheral vessels) is not uniform. The connective tissue fibers show a fine loose meshwork with clear spaces. Occasional cells of a lymphocyte type are also present, but every evidence of a fatty degeneration is wanting. The internal elastic lamina is usually uninvolved, showing neither splitting nor degeneration. At other times this elastic layer appears granular along its inner border and does not stain uniformly opposite the point of subendothelial thickening. These mild reactions are readily overlooked. The media is uninvolved, save where an occasional vasa vasorum shows a mild edema or collection of a few lymphocytes and plasma cells.

The stellate connective tissue cells of the intima are best seen in the sections cut on the flat. Here they show a meshwork with fairly wide spaces, looking not unlike the fibrous tissue cells of cultures in vitro as have been described by Burrows, Weil, Lambert and Hanes and others. The wandering cells are most frequently found near the surface while few are seen, in the early stages, at the inner border of the media. At this period, too, there is a comparable reaction about the vasa vasorum. This, as we have on a former occasion described, begins in a loosening of the stroma about these small vessels in the adventitia and media, and accompanied by a few lymphocytes and occasional plasma cells and leucocytes. It is to be recognized that normally a few lymphocytes are found about some of these vasa in the adventitia,

but their uniform presence about the majority of nutrient vessels, as well as their occurrence with plasma cells and leucocytes in the outer portion of the media, must be appreciated as distinctly pathological, and in the light of an inflammatory reaction.

In the early stages, the reactions are isolated to the tissues of the intima and those immediately surrounding the vasa vasorum. No changes are to be observed in the inner portion of the media, so that an uninvolved tissue is found to lie between the reactions in the inner and outer portions of the vessel wall. It would thus appear that the early reactions in the intima and about the vasa vasorum are unassociated.

The intensity of the reaction in the intima is not uniform, but is distributed in irregular microscopic patches over the surface. In the aorta these areas are more frequent about the mouths of the efferent vessels, and are particularly frequent at the points of exit of the intercostal arteries. They are frequent just at the ridge over the mouth of the vessel, and commonly extend inwards for some little distance along the lumen of the intercostal branch. These plaques, however, become less frequent in the intima of the intercostal, as this vessel perforates the deep portion of the aorta and passes beyond its confines.

As the process advances the tissue changes become more marked. This is mainly observed in the greater infiltration of cells, lymphocytes, some leucocytes, and a few plasma cells. The greater number of cells are still observed near the surface, although the infiltration now occupies the entire depth of the intima and to some extent the neighboring border of the media. This infiltration is fairly diffuse in the involved plaque, with, besides the more marked aggregation at the surface, occasional groups of cells in the meshes of the connective tissue. Where these groups are found there may also be observed the presence of large mononuclear cells, with vacuolated protoplasm bearing a resemblance to the lutein type of endothelial cells. These large mononuclears lie in groups in the connective tissue of the intima, and in the early plaques are best seen in sections cut on the

flat. With the appearance of these large mononuclears, degenerative changes may be observed. These cells in themselves contain much fat-staining material, and even though the cells are loaded with fat granules, the nucleus remains centrally placed. Free fat is not seen in any part of the intima and no evidence is at hand to indicate that the fat is deposited by a mechanical process as was suggested by Ribbert and Aschoff. On the other hand, other degenerative processes are also occurring in the tissues. The connective tissue fibers are no longer as distinct, but are aggregated in masses of matted fibrils which appear swollen and indistinct. A hyaline appearance is overshadowing the fibrous tissue structure. Fat may also be demonstrated in some of the connective tissue cells, forming wedges of deposit at the ends of the nuclei. Here and there, the elastic bands of the deep layer of the intima have lost their typical staining and are found to contain a fatty material which stains diffusely in the swollen bands.

Other than a somewhat more marked cellular infiltration about the vasa vasorum and the presence of a few wandering cells at the inner border, the media shows little evidence of further change. Evidence of degeneration is only present in the muscle cells and the elastic fibers of the media in the immediate vicinity of the vasa vasorum.

With the development of early fatty degeneration in the intima there is observed a change in the elastic elements in the outer portions of the intima. In the aorta and still better seen in the larger peripheral vessels the internal elastic lamina undergoes splitting. The elastic lamina becomes granular and may even show the presence of fat in the areas of degeneration, while the muscle fibers on its inner side appear more prominent through the presence of fine fat droplets within them. In our preparations the splitting of the elastic lamina and the early development of a fatty degeneration in the cells of the immediate vicinity, though appearing a little later than the first changes in the inner connective tissue layer, are a progressive accompaniment of the inflammatory process. The development of fine elastic

fibrils, in the intermediate zone between the intima and the media and which extend later into each of these layers, is also an early reaction in these lesions.

In the later stages of the systemic disease much of the reaction, particularly the edematous swelling of the intima and the cellular infiltration, may disappear. This is particularly evident in the disappearance of the visible intimal change after typhoid fever. Almost complete restitution of the tissues results. Even much of the products of degeneration is removed so that neither fatty deposits nor hyaline change can be recognized on the posterior wall of the aorta where they are prone to occur. On the other hand, even where naked eye evidence of perfect repair presents itself, some permanent alteration of the tissues of the intima may be recognized microscopically. The superficial layer of connective tissue of the intima is slightly increased in amount forming a thin laminated structure parallel to the surface. An increase in very fine fibrils of elastic tissue is also evident in the intima as well as in the inner media adjacent. Furthermore, the not uncommon splitting of the inner elastic lamina remains as a permanent alteration, though the accumulation of fat granules in the different types of cells may, to some extent, disappear.

The presence of new connective tissue in the intima becomes definite with the progress of the lesions, and in some specimens it would appear that a certain amount of hyperplasia of the subendothelial layer continues even after all evidence of the acute stage has disappeared. The reaction which takes place is a process lying entirely within the intima and does not result as the organization of an exudate upon the inner lining of the artery. Moreover, although wandering cells, chiefly of the lymphocytic variety, constitute the early reaction, a true process of interstitial organization is not the mode of repair in the intima. We have not observed the presence of capillaries in this structure, nor any attempt on the part of the vasa vasorum to send branches towards the lesion in the intima. The tissue changes are progressive and the connective tissue cells take part directly by proliferation.

At the withdrawal of the wandering cells, the new connective tissue establishes itself as a permanent mass of new fibers forming a greater or less thickening of the coat.

In the specimens of older individuals, evidence was at hand of a former connective tissue thickening of the intima. These were accompanied by tissue changes of degeneration as are commonly observed in chronic endarteritis. In some, the deep fatty change was evident to the naked eye, while the connective tissue hyperplasia formed a hyaline pearly plaque over it. Moreover, the various types of change in the musculo-elastic layer were recognized in many. In such specimens it is impossible to say in what manner the old endarteritic process was brought about. Was it primarily the result of an inflammatory reaction as we have indicated in the above observations, or did it develop only as a connective tissue hyperplasia, secondary to the fatty deposit in the deep layer? That the latter type of reaction does occur in the intima we feel fully convinced and have previously discussed elsewhere.

However, in the present series we have observed that the areas of old connective tissue thickening of the intima may become the seat of new and more acute reactions. An infiltration by wandering cells begins from the surface and extends into the superficial connective tissue which has again become quite loose. The reaction may remain quite superficial or may advance deeper into the old connective tissue plaque. The area of fatty degeneration in the base of the lesion may show the presence of a lymphocytic infiltration in the surrounding stroma. It is, however, of particular interest to observe the reactions which take place in the upper layer of the intima, where the progressive changes simulate those previously noted in younger individuals. The infiltration by cells, though mainly lymphocytic, also contains plasma cells and occasional leucocytes. Passing through stages of edema and infiltration it can finally be seen that a new increase of connective tissue has taken place. This new hyperplastic layer lies as a cap over the former compact and hyaline connective tissue area of the intima. Thus old lesions may become the site of new attacks of endarteritis.

It has been repeatedly indicated and more particularly discussed by Jores and later by Aschoff that the amount of the superficial connective tissue layer is not constant, and that at different ages a considerable variation may be noted. Thoma laid particular stress on the progressive increase of this connective tissue in the " nabelblutbahn," which may be looked on as a physiological process. Subsequently others have found that this connective tissue growth is not isolated to the " nabelblutbahn " system but may be seen in varying degree in other arteries. Moreover, Jores has pointed out that a sharp demarcation of this physiological growth of connective tissue cannot be made from the early pathological processes of this subendothelial layer. He does, however, insist that when the growth of connective tissues not alone involves the superficial layer but also spreads into the deep musculo-elastic layer, the process is always a pathological one.

The presence of the physiological connective tissue increase is not accompanied by degenerative changes, but when hyaline change is observed in the superficial layer or fatty degeneration is present in the deep portion of the intima, a simple process of tissue growth is not to be thought of. We would, however, indicate that all forms of fatty degeneration found in the intima in association with a connective tissue overgrowth are not a common process. As Jores has shown, a mixed type of hyperplasia of the musculo-elastic layer showing fatty degeneration with a superimposed connective tissue " regeneration " is not uncommonly noted. Furthermore, however, fatty degeneration may accompany the process of connective tissue growth of the intima without any involvement of the musculo-elastic layer. These degenerative changes are found in the connective tissue cells and in the large endothelial-like cells, which aggregate in small groups in the tissues of the inner layer of the intima. The presence of fatty deposits within the elastic fibers of the intima has also been observed in the absence of proliferative changes in the musculo-elastic layer.

Jores has restricted the term arteriosclerosis to the one type of intimal change in which an hyperplasia of the

musculo-elastic layer and a splitting of the internal elastic lamina is accompanied by fatty degeneration of the longitudinal muscle fibers. Where a superficial thickening of the connective tissues occurs over this process it is viewed by him as always secondary. Furthermore, the fatty degeneration which develops in the layer of connective tissue thickening is viewed as secondary to degenerative processes in the deep musculo-elastic layer. From our observations this does not always appear to be the case. We have repeatedly seen proliferative changes in the superficial connective tissue without involvement of the musculo-elastic layer, in which the newly developed tissue showed fatty deposits in the connective tissue cells as well as showed the presence of cells apparently foreign to the intima, the large lutein-like cells, which were loaded with fat. Under the Virchow classification, this would constitute a simple fatty degeneration of the intima, a passive process as opposed to atheroma which develops in the deepest part of the intima and is viewed as an active process. We must agree that in this stage of fatty degeneration when the fat is still contained within living cells the term atheroma is inapplicable, and it is even more than probable that many of these cells containing fat may recover their normal function with the disappearance of much fat from the tissues. On the other hand, a continuation of the deleterious influences upon the vessel wall must bring about destruction of the involved cells with the deposition of free fat in the tissues. Such deposits must be viewed as atheroma. Furthermore, the presence of these masses of free fat may further stimulate, as is suggested by Jores, Faber and others, the further proliferation of connective tissue in its vicinity.

I would draw particular attention to the presence of the large endothelial-like cells (lutein-like cells) which occur in the connective tissue layer of the intima under conditions of proliferation. Much has been said by recent observers concerning the presence of these cells in the vessels of experimental animals fed with cholesterin and lipoids. In fresh preparations doubly refractile lipoid bodies (cholesterin-esters) have been demonstrated within these cells

(Anitschkow). Similar cells may commonly be demonstrated in human arteries where the fatty degeneration occurs in the superficial layers of the intima, and when such specimens are cut (frozen) on the flat, they are seen as compact aggregations in which the lipoid substance is almost entirely intracellular. That this type of fatty degeneration of the intima forms an important factor in the subsequent development of atheroma, even in the absence of hyperplasia and degeneration of the muscle layer of the intima, appears obvious.

Rokitansky was among the first to view the nodular thickening of the arteries in the light of a pseudo-inflammatory process, although he did not believe that the intima itself, being a nonvascular tissue, was capable of undergoing true inflammation. The intimal plaques, he believed, were the result of a blood deposit upon the surface, which subsequently became converted into a tissue mass by cells derived from the blood. Others soon opposed this view, Engel, Crisp, and Naumann each finding that the intima was capable of an inflammatory process. Particularly, however, was Rokitansky's attitude attacked by Virchow, who not only demonstrated that the intima, like other nonvascular tissues, may be the seat of inflammation, but that a proliferation of its own cells leads to the nodular masses on the surface. He compared nodular endarteritis with chronic endocarditis where an inflammatory thickening results mainly in connective tissue proliferation without an extensive cellular infiltration. Cohnheim, Engelhardt and others also accepted this view, differing, however, in minor points respecting the origin of the leucocytic infiltration. Traube found that the white cells, infiltrating the intima, were derived directly from the blood stream, while Friedlander and Koester believed their origin to be from the vasa vasorum. Koester's findings are particularly interesting in that he noted the simultaneous cellular infiltration about the vasa vasorum and in the intima. His descriptions even indicate that under inflammatory conditions the capillaries of the media extend closer to the intima, and a rich lymphatic system extends from the media

to the intima. While the acute inflammatory processes were accompanied by a round cell infiltration, he observed that a connective tissue proliferation was present both in the intima and about the vasa vasorum in the chronic stages.

Our own findings have led to conclusions which, to some extent, are similar to those of Koester. The simultaneous presence of a small cell infiltration in the vicinity of the vasa vasorum and the intima may be observed during the acute stages, but we have not been able to demonstrate a constant relation between them in the arterial wall. The localization of one or the other in the artery is not always accompanied by a similar reaction in the other arterial coat opposite to it. In other words, though an inflammatory reaction may be demonstrated about the vasa vasorum in the adventitia and outer portion of the media, a similar process may not lie opposite to this in the intima. Moreover, where the simultaneous presence of a cellular infiltration has been observed in the inner and outer coats of the artery, there has always appeared a strip of media adjacent to the intima which was uninvolved in the inflammatory process. It would, therefore, appear that these reactions are individual, though frequently occurring side-by-side in the same vessel. The cellular exudate found in the intima appears to arise by a direct migration of the wandering cells from the surface of the artery.

Wiesel has made some interesting observations upon the arterial system of individuals under twenty-four years of age who had suffered an acute infection (scarlet fever, pyemia, diphtheria, typhoid fever, pneumonia). A variety of reactions of an inflammatory nature along with degeneration of the muscle cells and the elastic fibers was noted. He suggested the name " arteritis chronica postinfectiosa " for this condition which he believed was not related to arteriosclerosis. Faber also observed a variety of degenerations in the aorta after acute infections, and he suggested that the injury to the media, "dilatation, hypertrophy and hyperplasia of the entire vessel wall might occur." Hansen had recorded similar findings, but, going even further, stated that the acute infections had a direct influence upon the development of atheroma.

In Prag, Simnitsky also had his attention attracted to the presence of intimal thickening, degeneration (fatty), splitting of elastic fibers, in the aorta of young persons who had died of acute infections.

Although inflammatory reactions have been observed in the inner part of the intima under a variety of infectious diseases, the outcome of the process is not the same in all cases. Gradations of intensity of the primary inflammatory process may be observed in the early stages, while the nature of the repair in the older lesions also varies. As we have indicated, it is probable that many of the milder reactions, seen in the acute stage, may disappear without leaving recognizable change, but it is impossible to indicate from the appearance of a given lesion the subsequent outcome of the process in the arterial wall. Inflammatory reactions of the intima of longer duration are always accompanied by a connective tissue disturbance of a proliferative kind, and from them there develop the intimal thickenings of the " hyaline " type. These reactions are frequently of the pure connective tissue variety, but are sometimes associated with hyperplasia of the muscle layer of the intima and splitting of the elastic lamina. Nevertheless, the splitting of the elastic lamina cannot alone be taken as an indication of a hyperplasia of the deep muscle layer, as we have seen it in pure regenerative processes of the inner coat where no proliferative response was seen in the muscle tissue of the intima.

It is obvious that with the degree of the reaction in the intima, the component tissues will take part in bringing about a structural alteration in the involved area, at times proliferative, at others degenerative in kind. When, however, the harmful influences (particularly bacterial toxins) are so great, the proliferative changes give way to processes of degeneration of which the fatty is most easily demonstrated, and which may be recognized in a variety of tissues and cells. Whether all well defined processes of fatty degeneration of the intima shall be called atheroma finds no common agreement. For my own part, when the fatty degeneration of the intima has proceeded to that stage, that not alone

do we find fatty substances within the cells, but also that some of it has been liberated, by the death of cells, into the interstices of the tissue, giving rise to a free greasy deposit, do I speak of it as atheroma. Other products of degeneration, particularly the calcareous, are also mixed with the atheromatous deposit. From our observations it is clear that this atheromatous material may arise not only from the destruction of one type of tissue (deep intimal muscle), but also from degenerative changes in the elastic fibers, connective tissue, and the endothelial-like (lutein-like) cells.

CONCLUSIONS.

It would appear from the present study that contrary to our opinion previously expressed, the reactions in the intima, in many acute infectious diseases, may occur independently though simultaneously with the inflammatory reactions about the vasa vasorum.

The intimal reactions of the aorta are more marked about the mouths of the smaller vessels, particularly the intercostals, but they do not usually advance along the lumen of the branching vessel.

The reaction is an inflammatory one, in which the infiltration of wandering cells (lymphocytes and some plasma cells and polynuclear leucocytes) may best be observed when the tissues of the intima are cut on the flat.

The inflammatory process is accompanied by progressive as well as degenerative changes in the tissues of the intima. Repair is accomplished by a proliferation of the connective tissues of the inner layer of the intima and may show some hyperplasia of the musculo-elastic layer.

Splitting of the internal elastic lamina into multiple bands occurs in reactions of a purely inflammatory nature in the absence of hyperplasia of the deep muscle layer.

Fatty degeneration is a common accompaniment of the pure connective tissue thickening of the intima, and is found to involve particularly the connective tissue cells, the elastic fibers, and the endothelial-like cells found in the intima.

Deep areas of degeneration also show the involvement of the muscle cells of the intima.

The late stages of the lesion cannot be differentiated from processes of atheroma with superficial endarteritic thickening. It is superfluous to differentiate atheromatous softening of the intima by the particular tissue cells which show fatty degeneration and which on subsequent destruction liberate fatty materials in the intima of arteries.

It is probable that the structural changes brought about in the intima of the arteries in infectious diseases are the result of bacterial toxins, but it is possible that a vicious circle is set up in the affected area by which nutritional alteration and decomposition products of tissues also exert an influence upon the surrounding parts.

The entire process must be classed as one of arteriosclerosis in which proliferative and degenerative reactions are closely associated.

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PULMONARY ANTHRACOSIS—A COMMUNITY DISEASE.

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PULMONARY ANTHRACOSIS*—A COMMUNITY DISEASE.

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Definite observations upon the presence and nature of pigment within the lung substance and its associated lymphatic structures are of relatively recent date. Nevertheless, as early as 1717, Ramazzini discussed the presence of carbonaceous material within the lung and indicated an association with definite pulmonary diseases. His observations were made upon various laborers who, through the inhalation of angular stone particles, became predisposed to asthma and tuberculosis. His observations, however, did not suggest that any of the foreign material contained within the lung, consisted of a carbon deposit.

Not until Pearson in 1813 studied the problem and applied the term anthracosis or coal miner's lung, followed by a report by Laennec in 1819, was a more acute attention attracted to the subject. Pearson indicated that individual coal particles when inhaled became deposited in the lung tissue and upon the accumulation of larger quantities of this pigment, the lung gave macroscopic evidence of its presence.

This contention was further supported by Gregory, who in 1831, described the pigment in the lungs of a coal miner, with definite tissue changes within the organ. Other English authors (Thompson, Simpson, and Stratton) made similar observations and indicated the importance of anthracotic deposits as a type of occupational disease.

Although Pearson's views were accepted in England, they were strongly combatted in Germany, particularly by Koschlakoff, as well as by Virchow and Henele who regarded the coloring matter in the lung substance and in the lymph nodes of haematogenous origin. Virchow did not believe that the lung substance could be penetrated by inert foreign particles. As late as 1855, Barthelmess discussed "pulmonary melanosis" as a progressive pigmentation of the lung resulting from repeated hæmorrhages and inflammation. Subsequently, however, Pearson's observations were confirmed in Traube's clinic (1860) where some carbon pigment, presumably having its origin from charcoal, was demonstrated in the lung substance. Since then the deposition of carbon from smoke has been amply confirmed by studies upon human lungs as well as by animal experimentation. The first confirmatory animal experiments were carried out by Knauff (1867) and repeated by Konradi (1869).

In the earlier discussion upon the inhalation of dust, including the carbon particles of smoke, it was indicated that as every one inhaled more or less of it during his life time, little pathological change, other than the storage of pigment, occurred in the lung tissue. It was, however, recognized that the inhalation of different foreign substances had a varying effect upon the respiratory organs. It was deemed that carbon pigment had the least harmful effect and hence, the deposits which were found in the adult lungs, could be disregarded as having any association with respiratory diseases or clinical symptoms during life.

With the admission that the black pigmentation of the lung was the result of the inhalation of carbon particles contained in the air, a considerable controversy began concerning the manner in which the foreign material made its entrance into the tissues. It was not uncommonly observed that the sputum of individuals working in smoky atmospheres would, for considerable periods of time, contain black pigment particles. Some of this foreign material was free, while some was contained within cells. Knauff believed that these cells were desquamated epithelial structures of the bronchi, which had lost their cilia. It was thought that with the active desquamation of the epithelial lining that a more ready access for the pigment to the deeper structures was possible. Sikorsky and Klein both believed that foreign particles were able to pass between the uninjured epithelial cells and directly enter the lymphatics.

On the other hand, Arnold and Schottelius opposed the view of the direct migration of the pigment into the tissues and claimed that the transport was accomplished only through the agency of cellular activity. This phagocytosis they believed could be accomplished by the bronchial epithelium, lymphoid wandering cells and by the alveolar epithelium. Traube thought that the acicular nature of the carbon particles would account for their tendency to pierce the delicate alveolar walls and then to migrate to other parts by the lymphatic channels. Rindfleisch accepted this latter view, laid stress upon the gritty hardness of the particles and believed that through the impact of the air current the particles may be driven through the superficial tissues. He furthermore pointed out that when these foreign particles had entered the lymph spaces they not uncommonly became incorporated within cells having phagocytic properties.

The theory of the phagocytic transport of the foreign particles continued to gain ground but there was no agreement concerning the nature of the active cell. Slavjanksy and Ins believed that the leucocytes were most active, while Ruppert, Schottelius, and others believed that the alveolar epithelium picked up the carbon from the air sacs. Arnold was divided in his views, considering that both types of cells were capable of carrying out this function, while, furthermore, he believed that under certain conditions migration of pigment might occur in the absence of phagocytic

cells. Even to the present time, observers are not in unison concerning the taking up and storage of the pigment which reaches the lung. The exact nature of the phagocytic cells, and these seem to be the active participants in the accumulation of carbon pigment in the pulmonary structures, is still in debate. In a recent study, however, it appears to us that Haythorn has conclusively shown that although pigment may appear in a variety of cells, the important cell acting as a carrier from the air sac to the interstitial tissue and the lymphatics of the lung, is an endothelial cell.

Although, in the early days of cellular pathology (1858) the finding of extensive pulmonary anthracosis was unusual, the situation has changed much in the present day. Then as now, the most intense examples of pigmentation of the lung were found among the coal miners, and it was particularly to these that Pearson, just a century ago referred, when he first applied the name anthracosis to the pulmonary condition. Apparently, early in the last century, in the course of ordinary life the accumulation of pigmented dust bodies within the lung was hardly sufficient to attract the attention. At that time, the use of coal was less general among the housekeepers and the combustion of wood was relatively complete, with but slight pollution of the air. Then, too, coal was not in as general use in industries nor had the use of the steam engine found a definite place in manufacture.

Today, the use of coal forms the main source of energy for the remarkable industries which began in the middle of the nineteenth century. We need not indicate by figures or statistics the extent to which our progress is determined by the use of coal. Nor is it within our province to indicate, the enormous losses entailed in the incomplete combustion of coal. The main fact stands before us today that in every city where householders use coal or in which manufactures of any capacity are located, the air shows a greater or less pollution by carbon particles. Today, it is almost possible to gauge the extent of the manufactures within a city by estimating the quantity of carbon in the atmosphere. In other words, what, not so many years ago was a rather unusual aërial condition, today forms a constant finding and has added a nuisance which affects the well-being of the community. No longer may we regard the presence of carbon in the air of large cities as a harmless factor. And furthermore, the gradual accumulation of this foreign material within the respiratory tract has a definite effect upon the tissues in reducing their functional activity and in possibly leading to secondary disturbances affecting our general bodily health.

The following observations have been made upon a series of autopsies, in which the deposit of carbon pigment within the lungs was particularly noted. These observations were made upon civilians not engaged in coal-

mining. The majority of them had been residents of the Pittsburgh district for the greater part of their lives. We were unable to account for the great variation, which occurred in the intensity of the pigmentation among the different individuals, particularly when their respective occupations appear to have had no relation to the amount of the pigment deposit in the lungs. Thus one of the most markedly pigmented lungs was obtained from a peddler, in whose history we could find no particular association with a sooty atmosphere or industry. It is possible that the tissues of different individuals store the foreign particles from the air with different degrees of activity.

Admitting that but few individuals today can escape the accumulation of carbon particles in the respiratory system, it may be suggested that the condition should be looked upon as a normal process. This attitude has been the dominant one in the discussion of pulmonary anthracosis. As, however, we must today freely admit that individuals living under different circumstances and in different communities suffer unequally from the quantity of inhaled dust, it is impossible for us to designate all of these as normal conditions. That a small amount of anthracosis of the lungs is not incompatible with good health is obvious to all who have observed the condition in many autopsies. That, however, certain communities are subject to greater pollution of the air by smoke than others, and that the individuals in these communities suffer in an equally greater degree from the inhalation of soot and smoke is also obvious to those who have had an opportunity of comparing the lungs from different localities. The pathologist has no difficulty in recognizing lung specimens from large manufacturing cities.

Thus we are able to observe variations from the almost non-pigmented lung tissue obtained from those living far distant from cities, to the more intensely pigmented lungs, the coal miner's lung illustrating the extreme degree of carbon deposit. There is, however, some difference between the deeply pigmented coal miner's lung and that obtained from the city dweller. The carbon dust as inhaled in the coal mines is considerably coarser than the fine particles of soot found in the city air. Moreover, the dust in coal mines is made up of fine angular and rough particles, while soot is a mixture of a very fine amorphous carbon and ash.

ANATOMICAL CONSIDERATIONS.

The deposition of carbon pigment in the lungs from the dust-laden air is dependent upon the respiratory function and the activity of the lymphatics. The inhaled air with its carbon particles is carried to varying depths into the lung tissue. The major amount of the foreign material adheres to the moist walls of the respiratory passages and never reaches the lung tissue proper. It is possible, and microscopical analysis seems to

confirm this, that the foreign material that adheres to the mucus membranes of the nose, pharynx, trachea, and larger bronchi is but rarely carried into the tissues of these tracts, but lying in the secreted mucus, is carried upwards and is eventually expelled. The relatively lesser quantity of dust and carbon which reaches the lung alveoli also becomes adherent to the moist surfaces of the alveolar sacs and then by the activity of certain cells which have been studied and described by Haythorn, these particles are eventually carried into the lymphatics of the alveolar wall where they are disposed of by the lymphatic system of the part. The subsequent distribution is to a great extent determined by the site of absorption within the lung. Thus the carbon particles which have found their way into the air sacs near the surface of the lung, gradually accumulate within the lymphatics of the visceral pleura, while the carbon which is collected from the more centrally placed alveoli, accumulates about the lymphatic channels which drain that particular area. The tendency of this absorbed carbon is to pass from the finer lymphatic channels of the alveolar walls to the larger passages, eventually reaching a lymph node where the onward progress of the particles is impeded by the filtering action of this structure. In the main, the lymphatic drainage of the entire lung converges at the hilus and passes into the peri-bronchial glands located in this part.

The lymphatics of the visceral pleura form an intricate network, of channels which surround each lobule. The lymphatics upon the pleural surface of these lobules can, at times, be recognized by the naked eye. Many anastomoses occur and the larger channels drain towards the hilus. Communications between the surface lymphatics and those within the organ have also been demonstrated.

A somewhat similar system of lymphatic channels have been demonstrated about those lobules which lie within the lung. Not only is there a system of lymphatic channels about the lobules but small passages extend into the individual alveolar walls. Sikorsky, as well as Wittich claimed to have demonstrated small patent communications between the lymphatic channels in the alveolar walls and the air sacs. By this means, it was suggested, that foreign materials within the air sacs could find a ready passage into the interstitial lymphatic system. In 1878 Rindfleisch suggested similar passages for the entrance of coal pigment into the lung tissues. He believed that the fine dust particles could pass directly from theair sac into the interstitial lymphatic channels without the intervention of phagocytic cells. He did appreciate the rôle of phagocytosis in the subsequent transpotation and storage of the foreign material. It would appear, however, with the more recent studies that the migration of the dust particles from the air sacs occurs only through the agency of certain wandei ing cells.

To thoroughly appreciate the progressive pigmentation of the lung

substance by the inhalation of carbon particles, the general mechanism of respiration, as well as the efficient lymphatic drainage of all the air sacs must be understood. The important conclusions of Beitzke and Most, that the lymphatics of the lung and visceral pleura have no direct communication with those of the head, neck, or abdomen, and the fact that carbon particles are rarely found in the circulating blood indicate that pulmonary anthracosis is developed through the activity of the respiratory functions alone. It is, therefore, quite out of place, here, to discuss the claims of Calmette, and his associates, for the origin of pulmonary anthracosis in the alimentary tract. A more extensive review and study of the relation of intestinal absorption to anthracosis is given by Montgomery. This author from his own experiments concluded that the respiratory route alone was the important one leading to pulmonary anthracosis.

DISTRIBUTION OF PIGMENT BENEATH THE VISCERAL PLEURA.

At first sight, when the lung is examined externally, the distribution of the deposit of carbon pigment seems to be irregular and without any association with the anatomical structure of the lung. The pigment is deposited in small granular masses, which, in their beginning, occupy areas less than of pin-head size. Sometimes it would appear that the deposit is in the nature of lines which, however, on slight magnification are found to be the coalesence of numerous small granular points.

As the deposit becomes more extensive, the pigment is found to follow a definite arrangement, and the anatomical structures which, in the non-pigmented lung are not visible, are mapped out by the deposit. Thus the sub-pleural pigmentation is found to pick out the septa dividing the lobules of the lung. This geographical marking is more particularly evident in the early stages of the pigmentation prior to the diffuse deposition of the pigment with the consequent obliteration of the early linear markings. Whereas in the early stages of the deposit, the septa of the lobules show fine linear deposits of pigment, the increasing accumulation of the carbon leads to an irregular thickness of these lines and the conversion of them into small chains of nodules or to the development of flat or shot-like masses in the sub-pleural tissues. Gradually the deposit extends from the septa into the tissues of the lobules until blotches of pigment become prominent. All gradations, from the finest hair-like lines in the septa, to diffuse pigmented areas in which the normal color of lung substance cannot be recognized, are not uncommonly seen in the same lung.

The macroscopic appearance of the sub-pleural tissues is a very good gauge as to the actual amount of carbon pigment contained in the lung. That is, with the deposit of such an obvious pigment no difficulty is experienced in distinguishing its presence or in gauging the amount present in each portion of the tissue examined. It is well, however, to recognize that the

amount of carbon pigment on the surface does not necessarily indicate the extent or distribution of the pigment in any part of the lung tissue.   There are factors arising with each lung and within each lobe which tend to modify the amount of pigment within the tissue.

Although the pigment follows the septa of the lung lobules, the distribution upon the surface is by no means uniform.   It has been repeatedly observed that the amount of pigment in the different lobes as well as in the different portions of the same lobe varies very considerably.   The distribution of the pigment in the sub-pleural tissues is dependent upon the course of the lymphatic stream.   But, as has been indicated by S. R.

Early Anthracotic Deposit along Interlobular Septa.

Haythorn, the presence of carbon pigment within the lung may have a marked effect upon the subsequent condition of these lymphatics.   Thus, as we shall discuss later, the deposition of carbon pigment resulting through the activity of certain phagocytic cells has a tendency to stimulate tissue changes which modify the architecture of the organ.   It is most probable that by this means the deposit occurring in the lung tissue does not always appear in the same characters but, according to the particular tissue reaction (fibrosis), a modification of the lymphatic system leads to an altered physiological process in which the amount of deposit may be increased or decreased.

In the examination of a series of lungs it soon becomes evident that there are certain areas in the normal organ, which become involved earlier than others, and which usually show the most intense pigmentation in the later

stages of the process.   Thus in young adults who show no evidence of other diseased processes in the lung, the pigment is more prominent in the apex of the upper lobe, the anterior border of the upper lobe, and the posterior border of the upper and lower lobes.   Even in these three areas the distribution of the pigment is by no means uniform, for in different individuals the grades of intensity of the deposit differ somewhat within these locations.

It is the usual observation that the least pigmented portions of the pleural surface of the lung are the diaphragmatic and the interlobar surfaces.   It .is not uncommon, however, to observe a sharp line of pigmentation separating the out surfaces of the pleura from the interlobar areas.   At the border of each lobe, as it lies in apposition to its fellow, there is a marked pigmented zone, more intense than the deposit upon the free surface, and serving as a boundary between the pigmented pleura and the non-pigmented interlobar surfaces.

The distribution of pigment in the apex of the lung varies according to the shape of the part and to the character of the dome of the chest cavity. As has been pointed out by Schmorl it is not uncommon to have an unusual prominence of the upper ribs and irregular folds of the parietal pleura forming bands which divide the otherwise round dome of the chest cavity into several smaller compartments.   These abnormal ridges are very common, but are not constant in their disposition.   Not uncommonly they pass from behind inwards and forwards crossing the dome in an arched and rather spiral direction, the anterior extremity passing towards the hilus of the lung.   At other times, folds of parietal pleura pass from behind upwards and forwards, crossing the highest points of the pleural sac. When these folds are marked, a definite depression is left upon the lung surface, particularly if the lung is unduly distended by emphysema or pneumonia.   This depression is observed in the nature of a groove looking not unlike the vertical grooves seen over the right lobe of the liver (Liebermeister's groove).   These grooves become more marked and more permanent with the age of the individual.   Not only do they present depressions in the soft and spongy tissues of the organ, which, in the early years of life, can easily be obliterated, but in the course of years they remain as definite areas of retraction where the lung substance does not expand nor develop equally with the rest of the tissue.   Thus in the apical grooves the lung tissue is inhibited in its growth and its functional activity is hindered by obstructing bands.   Moreover, the lung tissue opposite the depths of the grooves is prone to become fibrosed or to develop adhesions to the parietal pleura.
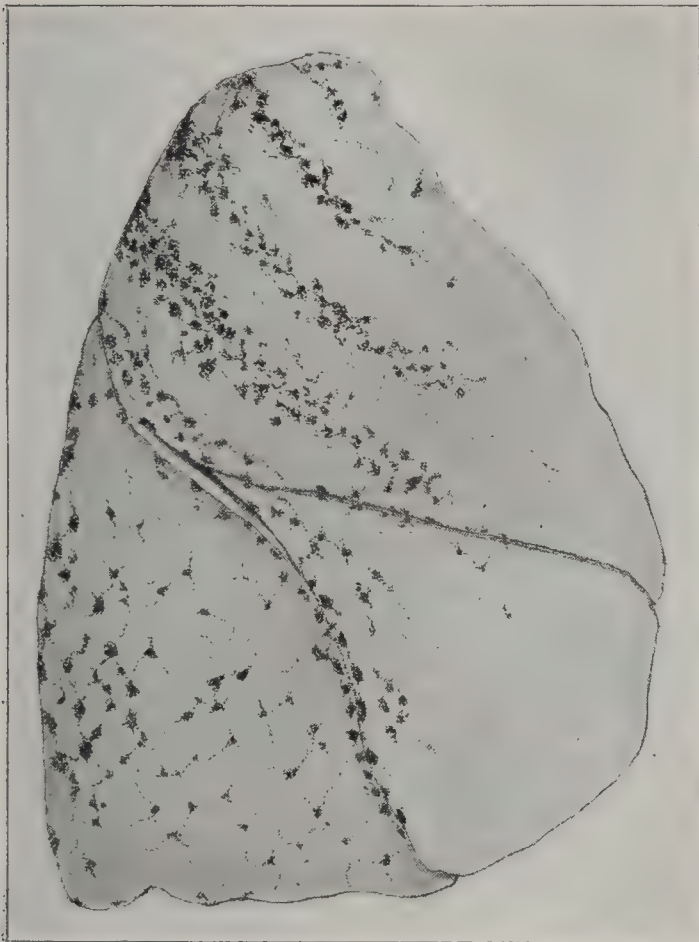
These apical grooves are also to be recognized in the variation of the deposit of the pigment.   The grooves when well marked attract the attention by showing a lessened amount of pigment than the surrounding tissue.   When several well marked grooves occupy the apex of the lung,

then this part of the lobe appears to contain decidedly less pigment than other parts. Yet on closer examination, although the apical pleura may appear to contain less pigment than the other pleural areas, this is due to the absence of pigment in the grooves themselves, and not to the variation of pigment in the parenchyma of the lobe.

The ridges bounding these grooves usually show an unusual pigmentation. The extent, however, of the deposit on the borders of the grooves is not uniform in that it is not uncommon to observe one border deeply pigmented while its fellow on the opposite side contains but little carbon.

The intensity of the pigmentation along the posterior border of the upper

Non-Pigmented Rib Grooves of Lung.

and lower lobes is commonly the most marked in the entire organ. From the early beginning of a tortoise shell marking indicating the division of the lobules, the condition progresses until the pigmentation produces one diffuse coloration of the pleural tissues.

Furthermore, there are two important considerations respecting the localization of anthracotic pigment in the pleura. The first of these is the relation of the pigment deposit to the position of the intercostal spaces and the ribs. The second is the relation of the pigment deposit to the opposed pleural surfaces between the neighboring lobes.

In respect to the relation of the pigment to the ribs and intercostal spaces there have been a number of views expressed. As above stated,

our attention has been particularly attracted to this question through the observations of Schmorl upon the apical grooves of the lung. Similar rib impressions are found in adults upon the surfaces of both the upper and lower lobes. Schmorl in 1901 indicated that the uppermost ribs produced individual impressions upon the lung substance which were easily recognized at autopsy. Schmorl found these depressions in children, but noted that they tended to disappear with advancing age. He believed that the depressions were the result of the undeveloped chest pressing upon the lung substance and that with the development of the thorax, in the normal individual, the pressure upon the lung was much relieved. He noted, however, that in these individuals, whom we are prone to look upon as possessing the anatomical character of a tuberculous subject, the flat chest, these grooves or rib depressions upon the lung remained permanently. Thus he believed that the anatomical characteristics of the chest altered the relationship of the lung to the pleural cavity which in the undeveloped condition was prone to bring about those anatomical changes of the lung, inviting tuberculosis.

The grooves in the lung tissue had the effect of compressing both the lymphatic and blood vessels. Likewise a certain interference might be produced in compression of the bronchial tree. These pathological conditions tended towards a stasis of the circulation of the part, permitting a more ready development of the tuberculous process.

It has, furthermore, been shown that not only do the ribs in the uppermost portion of the thorax leave their impression on the lung tissue, but that such marks may be distinguished for the entire series of ribs down to the 8th or 9th. These rib markings or impressions are more readily followed by observing the deposit of pigment by the actual depressions produced upon the lung substance.

As one will readily appreciate, the intensity of the impressions of the ribs upon the lung varies in different individuals. Not uncommonly, the thorax is of such dimensions or its capacity bears such a relation to the lung, that little or no effect of rib pressure is to be noted. Under those conditions in which the volume and consistence of the lung is increased, as in lobar pneumonia, the rib depressions are temporarily more decidedly marked.

Peiser has studied a series of cases and finds that the rib grooves are not well marked in the infant. In this he differs from Schmorl. He believes that the rib grooves increase in their depth as the individual assumes the upright position and the thoracic wall sinks. As the thorax, with increasing age, gradually assumes its new level, the upper ribs become more prominent on the inner wall of the thorax. These then produce depressions upon the lung surface. Not only does the sinking of the thoracic wall lead to the prominence of the rib margins, but the respiratory movements

are altered, there being a diminished respiratory activity established. This in its turn has the effect of producing a pulmonary stasis and a lessened elasticity of the lung. Peiser believes that with the altered condition of the respiration, the character of the lung substance changes so that the rib grooves are more readily produced.

Further observations have recently been made by Orsos. He studied the mechanics of respiration as regards the relationship of the expanding thoracic wall to the spongy lung substance within. He indicates that the thorax, constituting a closed cavity, has its walls made up of parts which are of different composition. In part, the wall consists of solid structures, the ribs, while in other places soft portions make up a part of the active walls. He points out that the effect of these two types of tissue upon the lung substance is different. The solid ribs, he believes, are more active in producing a suction by the expanding chest and a compression by the contracting chest wall. This greater activity in relation to a part of the chest wall has its effect upon the lung substance in that the tissue immediately opposite the firm ribs is functionally more active during the respiratory movements. The inactivity of the intercostal spaces is not only to be observed in the smaller alveolar spaces, but also in the more sluggish lymphatic drainage leading to the greater deposition of the insoluble carbon particles. Thus in the adult, the intercostal spaces become more richly marked by the deposit of anthracotic materials.

In discussing the views expressed by Orsos, an opposite stand was taken by Marchand, Aschoff, and Beitzke, in that each of them expressed his belief that the greater deposit of pigment occurred in the areas mapped out by the ribs.

In our own observations, we must, in the main, agree with the finding of Orsos. Some difficulty is experienced in determining which portion of the lung lay opposite the ribs, particularly when there have been no marked depressions, while the deposit of pigment is quite decided. There can, however, be no doubt as to the depressions opposite the first, second, or third rib, and in these situations, the grooves which are very decided contain less pigment than the high points of the ridges. At this point, however, it is necessary to introduce a word of explanation in discussion of the pigment deposit in and about the costal grooves. It is best to study those lungs which are moderately advanced in the anthracotic process, and which are not altered by the presence of adhesions. Inflammation introduces a factor which modifies the normal distribution of pigment so that we can no longer ascribe our findings to the influence of the costal grooves alone. We shall discuss the effect of inflammation upon the deposit of coal pigment at another place.

It is, furthermore, to be indicated, that the deposit of pigment along the intercostal areas is not uniform. Although the margins of the grooves as

well as the intercostal spaces contain the greater amount of the pigment while the depth of the groove is almost always free, it is impossible to make a common statement as to the exact outline of the deposit for each groove. No doubt, the intensity of the pigmentation is determined to a certain extent, by the individual characters, such as the prominence of the ribs, the corresponding depth of the groove, and the local pressure upon the lymph and blood vessels.

In support of the views of Orsos that the cavity of the grooves exhibit less pigmentation than the surrounding portions, is the fact that the natural depression as well as the opposed pleural surfaces between the lobes have the same characters as the rib grooves in being less pigmented than other parts. It is the common observation to find a pale non-pigmented pleura on the interlobar surfaces while the external visceral pleura is mottled by a pigment deposit. The same is true of the diaphragmatic surface. Here, too, a less amount of pigment accumulates. This variation in the distribution of the pigment upon the pleural surfaces is not dependent upon the difference of the respiratory function of the lung alveoli beneath these parts, nor is it due to a difference in the character of the distribution of the lymphatic channels which surround the lung alveoli, but it is dependent upon outer influences of pressure which modify the capacity both of the alveoli and lymphatics. In the normal lung these influences of pressure are to be observed mainly in the rib grooves, the interlobar and diaphragmatic surfaces. It is possible that the presence of points of pressure upon the lung tissue has the quality of massaging the parts during respiratory activity and thus driving the particles of pigment more rapidly to other parts. We are inclined to believe that this quality of massaging the parts by intermittent friction plays the important rôle of preventing the accumulation of carbon pigment in the given regions of the lung. As we shall point out later, the lack of flow in the lymphatic system does not prevent the accumulation of foreign particles. Stasis of the lymphatic system, although preventing the fluid within the channels from flowing with normal rapidity has little effect upon the migration of the cellular elements, which are the main means by which the foreign material is transported. Thus, although stasis prevents the proper flow of the serum through the lymph channels, it permits the wandering of phagocytes into the obstructed region where these may accumulate in undue proportion. These wandering cells with their pigment burden are the chief causes for the pigmentation of the given areas of lung tissue.

Interstitial Pulmonary Anthracosis.

The nature of the distribution of carbon pigment in relation to the pulmonary alveoli within the lung is very similar to that observed upon the pleural surface. We do not, however, have an opportunity of viewing

the pigment in the same manner. Thus, in a cross section of the lung we do not have the opportunity of observing the surface of the lobules, but see only cross sections of the partitions. Thus for the most part our attention is attracted to the deposition of pigment at the points where the partitions meet. In these situations we observe small nodular deposits not uncommonly the size of pin-heads. At first sight, it would appear that the amount of pigment within the lung is relatively less than that observed on the surface. Nevertheless, it can be observed that the total amount of pigment within the lung tissue bears a relation to the quantity observed on the surface. In the normal lung, however, the distribution within the tissue is more uniform than the distribution of carbon in the pleura and there is not the macroscopic variation in different parts of the lobes, save at the hilus where the parenchyma is more pigmented on account of the greater accumulation in small lymphatic channels and nodes.

Furthermore, the unequal distribution of the pigment as it is observed upon the pleural surface has no direct relation to the deposition within the organ. The lack of pigment upon the interlobar surfaces and in the rib grooves is only a superficial condition and does not affect the deeper underlying lobules. The earliest deposits of coal pigment are to be looked for mainly in the perivascular lymphatics of the smaller branches of the pulmonary artery, subsequently, pigment appears in the regions of the small bronchi and venules. In all of these situations, its presence becomes more marked with the increasing quantities of soot that are constantly inhaled.

As the accumulations of pigment gradually increase, they not only form lines along the septa of the lobules and the vascular channels, but nodular collections appear at the points of junction of the various lymph channels, where small receptacula are formed. These nodules become so prominent that they are readily felt by the finger, and at times the course of the lymph channel can be detected by the feel.

Tissue changes may or may not accompany these larger depositions of pigment. In the majority of instances, however, a process of fibrosis, not accompanied by any inflammatory exudate, makes its appearance and surrounds each pigmentary nodule. These can be detected by the naked eye, while the larger ones which are short-like and gritty, are commonly spoken of as "anthracotic nodules."

In none of our specimens were we able to observe any uniform variation in the deposit of the anthracotic pigment within the lung of normal individuals. The greater quantity of pigment along the various channels has been indicated above but no unequal distribution of pigment has been observed which would in any way correspond to the unequal distribution beneath the pleura. True it is, however, that certain pathological processes

in the lung tissue may modify the distribution of the pigment to a very great degree. We have, however, failed to find any evidence of excessive deposit in the deep tissues at the apex of the upper lobe. In fact, in our experience, more pigment was found toward the hilus than at the periphery, regardless of the pleural distribution. Furthermore, the more marked areas of pigment deposit in the pleura are confined to this superficial layer and do not involve the underlying parts.

In several specimens of lungs from elderly individuals, who showed a moderate amount of emphysema in portions of the lobes near the surface, it was observed that an unequal distribution of the anthracotic pigment was present. Those lobules showing emphysema contained less pigment than elsewhere. This condition was not only apparent by the greater area occupied by the emphysematous tissues but was real, in indicating less carbon in the affected tissues. When such emphysematous areas occupy the surface alveoli, and when these lie upon the ridges of the costal markings, it is then found that the borders of the grooves contain less pigment than the surrounding areas. Thus the contention of Marchand and others that the ridges between the intercostal grooves accumulate less pigment may have its explanation in the presence of these emphysematous alveoli.

The Modification of Anthracotic Deposits by Other Factors.

It is evident, from what we have said, that every individual has a greater or less quantity of carbon accumulate in the lungs, and that this accumulation varies in the normal lung according to the amount of carbon in the inspired air. With advancing age, the quantity of pigment continues to increase until a relative standard for the community in which he resides is reached. This pigment in the normal lung becomes deposited, through the agency of phagocytic cells within the lymphatics and its particular location beneath the pleura of the lung, is dependent upon the distribution of the lymph channels and the relationship of the opposed pleural surfaces which varies to some extent in all individuals. The distribution within the normal lung substance, appears to be entirely determined by the circulation within the lymphatics.

Whereas, under normal conditions we may look for certain common features in the anthracotic deposits in the lungs, there are also pathological processes which bring about a modification of the deposit. Thus we find that certain disturbances within the lung tissue have an effect of inducing greater deposits of pigment within localized areas. And it is probable that this new condition of excessive pigment deposit brings about further changes instituting a vicious circle.

Local Pleural Inflammation.—It is not an infrequent observation to find a greater quantity of pigment in the immediate vicinity of a band of

pleural adhesions. By some it has been suggested that these adhesions are the result of the unusual deposit which leads to an excessive irritation in the surrounding tissues. When, however, we study the development of pleural adhesions we find that the fibrous bands in children show little or no difference in the deposit of pigment from other parts of the lung. With advancing age, however, the accumulation of carbon at the point of attachment of the adhesion to the lung becomes greater. A difference is noted too, in the character of the adhesions, for those which have only a superficial attachment and do not induce a fibrosis of the neighboring lung tissue, show less deposit. It is obvious that we must differentiate those pigmentary processes associated with primary pleural adhesions from those that we associated with primary lung disturbances (tuberculosis), in which adhesions may also be present. Of this latter type we shall speak again.

The best example of pleural adhesions for study, are those developing between two surfaces which are in constant frictional contact, as well as the bands of adhesions which sometimes follow fibrinous pleurisy in early life. Of the former type, we meet with adhesions at the apex arising from a rib groove which, under ordinary cirumstances, is non-pigmented. Here a firm band of adhesion binds a portion of the lung to the chest wall. The fibrous band not alone attaches itself to the surface of the visceral pleura but bands of tissue enter to a greater or lesser extent the fibrous layer of the lung covering and the interstitial septa, and alveolar walls. The fibrosis spreads diffusely through the tissue surrounding the blood vessels and encroaches upon the loose tissue of the lymphatics. Some of the lymph channels become completely obliterated, others are altered in their course.

It is probable that some of these bands of adhesions develop without the presence of an acute process and like the presence of milk spots of the heart, induce a progressive fibrosis which alters the relationship of the surrounding tissues. The pleura with its vascular tissues is altered to a sclerosed structure in which the lymph channels are reduced to mere clefts. In this condition not only is there a stasis of the fluid within these channels but there is also a filtering out of the phagocytic cells which are constantly wandering from the alveoli towards the larger lymphatic system at the hilus. Gradually the accumulation of cells is sufficient to show the increased quantity of pigment within the part. It would appear, according to Haythorn, that these migrating cells may live for a considerable period with the pigment within their protoplasm. Other phagocytes probably liberate their contents which become deposited in the interstices of the fibrosed areas. It is probable that the liberated carbon remains in the clefts between the cells and does not enter fixed tissue cells.

If the opportunity for the absorption of carbon pigment from the alveoli

be great, then the accumulation of this foreign material in the vicinity of adhesions becomes very marked. Nodules are formed which are hard and encroach upon the lung tissue. The lung alveoli are surrounded by a progressive fibrosis containing much carbon. It is more than probable, that when such excessive quantities of pigment are deposited that these again act as irritants, inducing greater adhesions. We do not believe that the inhalation of carbon in the normal lung will induce pleural adhesions unless some other factor within or upon the lung acts as a primary exciting cause. We have, upon repeated occasions, observed the lungs of mill workers and coal miners in whom the lung tissue had become intensely black through carbon deposit without there being any evidence of pleural adhesions.

We have never observed that acute pleurisy altered the deposit of pigment in the pleura. It has been observed that in acute inflammatory processes where the lymphatic channels of the pleura are filled with migrating and phagocytic cells that a considerable amount of pigment may be removed from the pleura to other parts. The exact bearing which this inflammatory migration might have upon the total pigment content could not be determined. The changes, however, were insufficient to produce any difference in the amount of pigment to be noted by the naked eye.

On the other hand, the chronic processes of the pleura not uncommonly had an effect similar to that observed associated with individual tags of adhesions. In cases where there were universal fibrous adhesions, the effect was not observed in the quantity of pigment deposit except where denser bands had developed. The diffuse and veil-like adhesions were without change in the vicinity of their attachment to the lung. A study of these indicated that the fibrous tissue of these adhesions had only a superficial attachment and did not involve the deep layer of the pleura. Where, however, the intensity of the chronic adhesive pleurisy was not uniform and where irregular bands were attached to the lung substance at various points, a more marked pigment deposit was prone to form.

In all instances where the more intense deposit of carbon pigment was associated with bands of adhesions, the process remained fairly superficial and localized. There was no invasion of the deeper parts by the continuous accumulation of pigment.

Inflammation of the Lung Substance.—Much has been indicated to associate pneumokoniosis with acute and chronic respiratory diseases. As early as 1717, Ramazzini drew attention to certain air-borne occupational diseases, and since then the greatest attention has been paid to diseases associated with inhalation of dust. Naturally, much interest has centered about the effect of inhaled dust of various kinds upon the lung and more particularly the relation, if any, that existed between these changes brought about by the deposits and inflammatory processes induced by bacteria.

The manner in which this relationship was established has not been entirely clear. By many (Ascher and others), however, tuberculosis has been looked upon as a process secondary to the deposition of the dust.

On the other hand, the relative infrequency of pulmonary tuberculosis amongst those who are engaged in work associated with much coal dust, has been pointed out by a number of authors (Ogle, Sommerfeld, Hirt). In the statistics, tuberculosis appears rather rare among coal miners. It would, therefore, appear that the inhalation of coal dust does not predispose to tuberculosis. The explanation for this appears to depend upon the morphological characters of the dust particles. On the other hand, Kuborn, Villaret, Versois, and others believe that the continued contact with coal dust leads to a true immunity against tuberculosis. Racine believed that coal contains substances which are antiseptic and disinfectant, and that this quality inhibits the growth of the tubercle bacilli, and Holman has shown similar disinfectant qualities in soot. Another (Idel) believed that the porous coal dust absorbed the tubercle bacilli and rendered them inert, while Wainwright and Nichols thought the partially soluble calcium salts contained within the coal gave the animal body protection against these organisms. The indication that the presence of coal dust within lungs had a favorable effect upon respiratory diseases, led Guillot to use the inhalation of coal dust for therapeutic purposes. As early as 1793 Beddoes established a sanitarium near Bristol where he treated chronic diseases, as asthma and consumption, by the inhalation of charcoal. The patients were placed in a dusting box where by mechanical means the charcoal was distributed into the air. However, it was later shown by Papasotiriu that coal dust had no influence upon the growth of the tubercle bacilli upon glycerine agar cultures, while Cornet was unable to protect animals against air borne tuberculosis by means of the inhalation of carbon dust. It has been indicated by Bartel and Neuman that anthracosis increases the virulence of tuberculosis in experimental animal infection.

It is more than probable that the infrequent presence of tuberculosis amongst those developing extensive anthracosis has its explanation in certain anatomical changes in the respiratory system, and it is possible, as is indicated by Fraenkel and admitted by Racine, Wainwright and Nichols, that the infrequence of progressive tuberculosis among the coal miners is due to tissue obstruction of the lymphatic channels brought about by the anthracosis.

Ascher's observations that the extensive inhalation of smoke as well as soft coal increases the mortality in tuberculosis, is not in agreement with other general findings. It has, however, been shown by Hart that there is a difference in the composition of smoke particles and coal dust, and that the former contains some of the products of coal distillation. Again it has been shown by others that laborers engaged in atmospheres containing

much coal dust, such as stokers, coal heavers, and chimney sweeps, are just as immune as coal miners to tuberculosis (Markel, Versois). Lewin found that 92.3 per cent. of chimney sweeps who had followed this occupation for more than ten years were free from respiratory diseases.

Our own observations have concerned themselves in determining the influence of the pigment upon the lung tissue as well as its relation to the tissue changes in acute and chronic processes within the lung. We can offer no statistics which show the relation which the pigment deposit has to the occurrence of infections of the lung. This study also deals with the effect of certain respiratory diseases upon the subsequent deposition of carbon pigment.

As it has been shown that the anthracotic material owes its presence to the activity of certain phagocytic cells, it is evident that an interesting problem confronts us in determining what rôle similar cells stirred to activity by a bacterial irritant will have upon the foreign materials, as carbon pigment, which are already present in the interstitial tissues.

In the study of lung tissues showing acute pneumonia, one is confronted with the picture of a lesser pigmentation in the areas involved in the pneumonia. The appearance is quite decided, and a fairly sharp line of demarcation separates the pneumonic area from the more healthy tissues. Within the consolidated portion of the lung the carbon pigment is seen only in the more prominent nodular deposits, while the pigment observed along the interlobular septa in the normal lung can no longer be traced. The diffuse pigmentary deposit in the alveolar walls is also overshadowed by the color of the exudate, be this grey or red. However, when viewing the lung from its pleural surface, no change in the amount of pigment deposit is observed in the superficial portions.

Although a decided diminution of pigment within the consolidated area is apparent, the fact that pigment is actually removed from the tissue involved in the inflammatory process can not be demonstrated in the lung after its recovery from pneumonia. We have not been able to define the areas of consolidation after recovery from the disease, by the amount of pigment in the tissues.

It does seem, however, that some of the pigment in the lung tissue becomes dislodged during the active migration of cells. During the late stages of pneumonia, the lymphatic channels contain a greater number of pigment-bearing cells than are observed in the uninvolved lung. It may be that, due to the stagnation of the lymphatic system in anthracosis, these pigment bearing cells do not have an opportunity of migrating from the pulmonary structures but remain stagnant in the dilated lymph channels. The macroscopic appearances of a diminution of carbon pigment during the acute stages of the pneumonic process is more apparent than real, and

is due to the overshadowing of the normal lung structures by the cellular exudate of the inflammation.
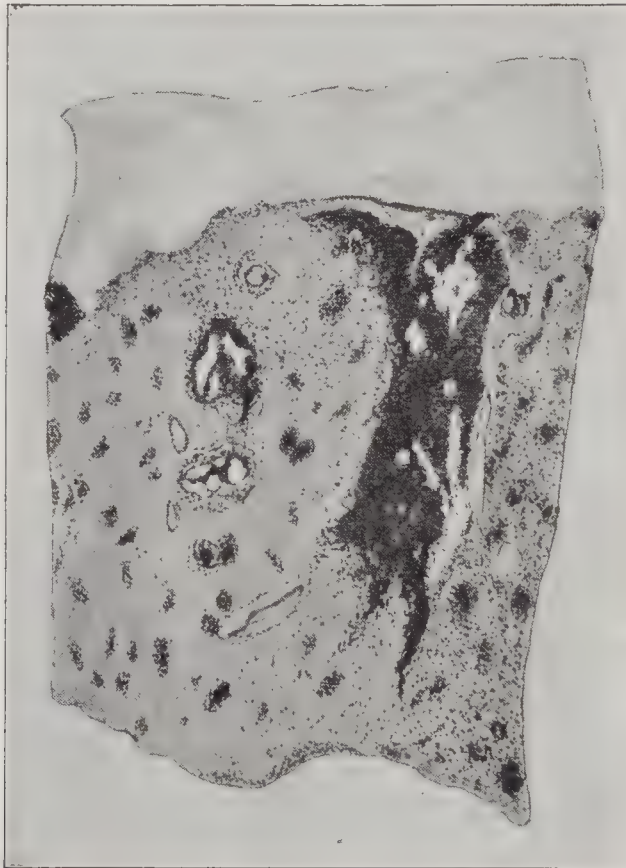
On the other hand, we have repeatedly observed that in isolated areas of fibrosis of the lung where no evidence of tuberculosis was found that the amount of anthracotic pigment was much increased over that present elsewhere in the same lung. We can, however, hardly offer this as an indication that the sequel to an acute inflammatory process, ending in fibrosis is associated with an excessive pigmentary deposit. In a single case of well advanced organized pneumonia we observed some increase in the the amount of macroscopic pigmentation within the fibrosed area, as well as microscopic evidence of such increased deposit. Naturally, it is difficult to estimate the exact variations from the normal deposit in different parts of the same lung.

In no instance has the examination of pneumonic lungs shown that the presence of the anthracotic deposit has, in any way, modified the distribution of the acute process. It cannot be shown that the more intensely pigmented tissues are more readily subject to pneumonia than the other less involved areas. It has, however, been suggested by Haythorn that aside from the local pigmentation in the vicinity of the individual air sacs, the anthracotic process of the lung has a definite effect upon the lymphatic system and particularly the lymphatic channels. These channels which become narrowed and partly obstructed, are less efficient for carrying off the débris which accumulates in the acute inflammatory process. This stagnation impairs the process of resolution with the result that proper repair of the lung following pneumonia does not take place. Conditions of unresolved pneumonia and gangrene of lung are more common in lungs with marked anthracosis than in the less affected organs.

We have in many examples made observations upon the anatomical relationship between the anthracotic deposit and tuberculosis. It is immediately apparent that in the discussion of such a relationship we must clearly define the type of tuberculosis. Naturally, the effect of the distribution of the tuberculous process upon the anthracotic deposit will be different in acute miliary tuberculosis than in chronic localized tuberculous lesions, and similarly the reverse relationship, if such exists, will also differ with the various forms in which one meets the tuberculous process. Individually, both processes are dependent, for their local distribution, upon similar factors, the phagocytic activity of cells and the distribution of the lymphatics.

We have not been able to observe any direct bearing of the anthracotic process upon acute miliary tuberculosis, nor have we observed a greater tendency for the development of tuberculous lesions in the anthracotic areas than in other parts of the lung. In fact, lungs showing moderate anthracosis will have more acute miliary tubercles in the uninvolved por-

tions of the lung than in the anthracotic nodules. Nevertheless, we have observed that in the later stages of the process when the miliary tubercles had advanced to larger and more definite caseating areas that the localized areas of anthracosis not infrequently had gray tuberculous centers. It is probable, therefore, that the absence of tubercles within anthracotic nodules during the acute stage of the infection is, in part, due to the intense pigmentation obliterating the early tuberculous focus. As the anthracotic deposit is associated directly with the course of the lymphatic streams and particularly with those surrounding the blood vessels, it is to be expected from what we know of the distribution of tuberculosis that many tubercles

Anthracosis of Lung about a Tuberculous Focus.

will develop along these systems, in spite of the presence of anthracosis. As the individual miliary tuberculous foci increase in size they gradually obliterate the anthracotic areas with the change from an intensely pigmented tissue to one showing numerous gray nodules of various sizes. With the increase in number, the tissue gradually loses the intensity of its pigmented appearance.

A still more marked loss of anthracotic pigment from the lung is seen in caseous pneumonia. Here, instead of having many small gray nodules gradually obliterating the pigment within the lung, we observe a diffuse gray caseous tissue whose light color is in strong contrast to the pigment in other portions of the lung. Only a moderate amount of pigment deposit is seen in the caseous area, and this pigment lies in the areas of former

intense deposit.   The grey color of the caseous areas not only represents the necrotic exudate within the alceoli but also indicates tissue changes, first proliferative, later degenerative, of the alveolar walls and their contents.   It is during the process of proliferation in the alveolar walls and lung trabeculae that the former pigmented cells are stimulated to proliferation and probably migration which leads to a removal of the pigment in the particular area.   What eventually becomes of the disturbed pigment in the lung tissue during the tuberculous process is difficult to say.   In part, it finds its way towards the lymphatics at the hilus of the lung.   In part, it may become removed by the destruction of the tissue and subsequent expectoration.

In the above processes, acute miliary tuberculosis and caseous pneumonia, it is evident that anthracotic process has no influence in localizing the infection.   We have, however, observed that miliary tuberculosis is more prone to develop into a chronic caseous miliary form in lungs presenting much pigmentation than in those not affected.

Quite a different outcome is observed in localized chronic caseous tuberculous foci.   The early stages of the tuberculous process simulates the lesions which we have just described.   As the lesion enters the chronic stage one observes that instead of there being a diminution of pigment in the involved area, that gradually, and in direct proportion to the amount of fibrosis, the pigment deposit increases.   Thus the periphery of the lesion, in which area the healing of the tuberculous mass is taking place, larger amounts of pigment are continuously laid down.   We have never observed the macroscopic increase of pigment before the development of fibrosis in the lesion.   Eventually the fibrosed mass becomes intensely black, and hard.   These areas vary in size from a pea to a mass the size of a golf ball. When fully developed, the tissue with its pigment deposit resembles in consistency and color a hard rubber ball.

We have observed all stages of these pigmented masses surrounding tuberculous foci and it is evident that the pigment deposit develops upon the tuberculous lesion.   The extent of the pigmented area is entirely dependent upon the reaction in the tissue of the tuberculous focus, and this reaction is always of the development of fibrosis.   Where a tuberculous process by progressive caseation has led to cavity formation, there is no excessive pigmentation in the vicinity of the cavity until repair by fibrosis has begun in its walls.

Microscopically, it has been shown that the same cells which form the tubercle and which in themselves are phagocytic for tubercle bacilli, are also the cells most phagocytic for carbon pigment.   Thus these cells constituting the tubercle are adapted for the localization of foreign dust particles, and being in excess of the number present in the normal parts of the lung may bring about an anthracotic deposit, with the tubercle.   However, by

the time the pigment has accumulated in sufficiently large quantities to be recognized macroscopically, there has developed a secondary fibrosis inducing a vicious circle by obstructing new lymphatics and accumulating greater numbers of pigment laden cells.

Tissue Changes Induced by Carbon Pigment Within the Lung.—Today we have come to recognize that the term anthracosis does not refer alone to the presence of coal pigment within the lung, but also includes the tissue changes which accompany this deposit. As we have previously indicated we have come to recognize that the deposition of the carbon in the lung is brought about through the agency of phagocytic cells. It is not probable that inert carbon can enter the lung tissues by mechanical means alone. The contention of Klein, Sikorsky, Merkel and others that the physical characters of the foreign material is such that it may migrate between the cells in the alveolar walls without the assistance of wandering cells can no longer be supported. Hence it is evident that the very process of accumulating and carrying the pigment is a vital one, and has to do with the cells arising from the pulmonary tissues. It has been shown that the number of cells acting as phagocytes found within the alveoli is proportionate to the quantity of pigment in the air sac and thus, too, the activity of the wandering cells is dependent upon the inhaled carbon. As the engulfed pigment is prone to remain fixed for considerable periods of time, it even being claimed by some that the phagocyted pigment remains permanently within the wandering cells, there is a progressive accumulation of these cells in the lymph spaces of the alveolar walls. Their direction is mainly towards the larger lymphatic system at the hilus of the lung, but it is also probable that these cells may not only lie inactive for varying periods of time, within the interstitial lymph spaces, but are still capable of returning to the air sacs to encumber themselves with still more foreign material.

How long these cells of an endothelial type are able to remain dormant but still living, is very difficult to say, yet it has been demonstrated in tissues that pigmented cells having every appearance of fixed connective tissue when thoroughly analyzed and segregated from their surroundings were found to be endothelial cells.

It is the common observation to find a progressive accumulation of pigment bearing cells within the alveolar walls with advancing ages. As the cells increase in number within the lymph spaces the wall becomes thicker and the tissue has a more or less hyaline appearance between the aggregations of pigment granules. To a certain extent the increase in tissue is the result of a direct increase in the number of wandering cells. On the other hand, we have also been able to show that there is a definite increase in the connective tissues about the lymph channels with the laying down of heavy collagen strands.

With this fibrosis there is no increase in the elastic tissue; in fact, the areas of extensive change are poorer in elastic fibers than normal.
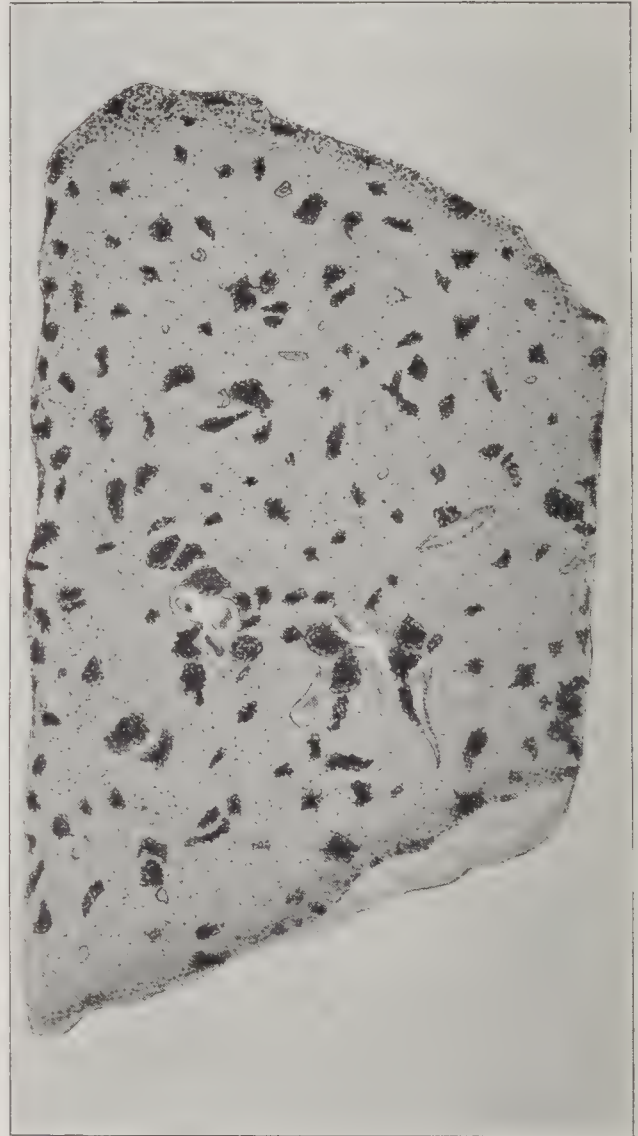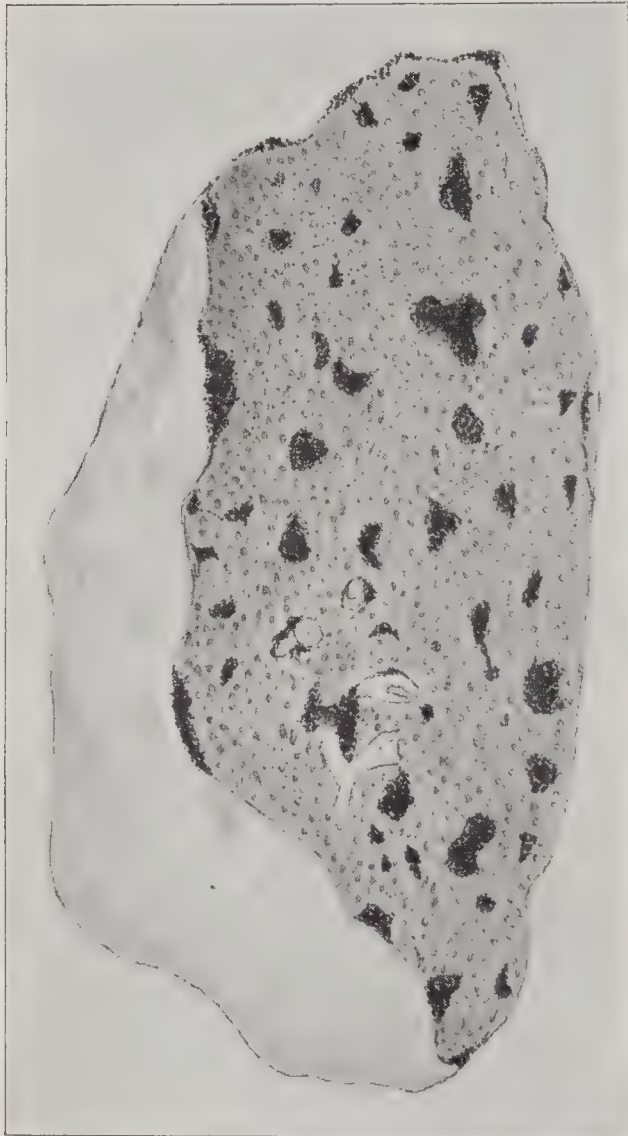
As we have previously indicated, the distribution of the inhaled dust in the lung is quite uniform, save for its distribution in the lymphatics of the pleura. Some (Arnold and also Boer) maintain that the deposition of soot is considerably greater in the upper lobe. This has not been our finding, though at times a difference has been observed between the two lungs. The accumulation of dust to that extent which induces secondary fibrosis will thus give rise to a fairly uniform tissue change in all lobes of the lung. This is a common finding inasfar as the lung tissue proper is concerned. It is probable that the fibrosis thus produced assists further with preventing a proper lymphatic circulation (Haythorn) and leads to the greater number of phagocytic cells becoming localized in the alveolar walls.

It is probable that the very nature of the phatocytic cells, being large and sluggish in activity, leads to their more ready localization in the lymph clefts than the more active leucocytes which deal with acute disturbances. If the normal functions of the endothelial phagocytic cells would be continuously carried out, it is improbable that as great a quantity of carbon would localize in the parenchymatous tissue of the lung, more of it finding its way to the large lymphatics and lymph glands at the hilus. The very condition which is brought about by the obstruction of the lymph clefts and small channels as well as the blocking of the lymph sinuses in the nodes about the bronchi tends to increase the localization of the large phagocytes close to the alveoli from which they obtain their pigment. Thus the nature of the pigment phagocytosis and the localization within the lymphatic spaces tends to bring about a vicious circle which, when a certain degree of anthracosis has developed, permits of a still more rapid deposit of pigment in the alveolar walls. It is about in this stage of the condition that the developing fibrosis leads to structural changes which impair the function of the lung tissue.

Other than inducing a diffuse fibrosis within the lung, there are also the nodular fibrotic masses surrounding accumulations of pigment bearing cells at the junction of the lymphatic channels. The more common of these are the size of wheat grains. The fibrosis assumes a concentric arrangement enclosing pigment which to a great extent lies free, but much of which is contained in the original phagocytic elements. Such nodules, however, may become much larger, forming isolated masses, three or four centimeters in diameter. It is probable, however, that these larger masses arising in the lung tissue have had other factors superadded, leading to their unusual development. The consistence of these is that of hard black rubber. Where calcareous masses are found in the center of such nodules, the previous existence of tuberculosis is strongly suggested. This asso-

ciation of anthracosis with chronic tuberculosis we have discussed above.

Anthracosis and Emphysema.—With extensive and diffuse development of pulmonary anthracosis in which tissue changes to a greater or less degree are developing, the activity of certain parts of the lung is impaired to such a degree that compensatory changes occur in other and more active parts. These compensatory changes are mainly evidenced in the development of emphysema. It would be difficult to indicate the se-

Nodular Dissemination of Anthracosis.

quence of events in laborers or coal miners. Here, from the very nature of their work emphysema would readily occur. We may, however, observe emphysema in individuals with diffuse anthracosis whose work or whose thoracic condition would offer no explanation, for the compensatory expansion of certain lung areas. This we have on several occasions observed, and we were unable to find an explanation save in the diminished functional activity in those portions of the lung with marked anthracosis and fibrosis. The development of the emphysema observed in the positions is seen under other conditions.

The apex and the anterior border of the upper lobe are usually most involved. A rather remarkable feature associated with this emphysema is the disappearance of the anthracoti pigment from the emphysematous area. Where the alveoli become usually distended the pigment gradually disappears until the tissues look quite white (pulmonary albinism). This has been commented upon by Beitzke and others.

From our observations it would appear that this loss of pigment from the lung is the result of the greater local activity during the process of development of the emphysematous areas. The condition would simulate the lack of pigment observed in the interlobar pleura where the massage of these areas by constant friction seems to drive the pigment bearing cells into the larger lymphatics. This is probably also the case during the development of the emphysema where the lung alveoli are acted upon by the greater air pressure having the effect of repeated compression and relaxation. Thus the air contained within the alveoli has the effect of massaging the alveolar walls and likewise of driving onward the cells containing the pigment. A similar effect would also be had upon the free pigment within the lymphatic spaces of the alveolar wall. In these emphysematous areas the removal of the pigment is not associated with an inflammatory process assisted by active leucocytic phagocytes.

QUANTITATIVE ESTIMATION OF CARBON IN LUNG.

As we have indicated, a fair estimate for comparison can be made of the carbon deposit by the naked eye appearance. The pleural deposit of carbon, although not directly related to the presence of pigment in the inner portions of the lung, is nevertheless, a good guide to the quantity of foreign material in the organ. The pale grey or greyish-pink color of the lung of the rural inhabitant is readily distinguished from the mottled, streaked or slaty black tissues of the city dweller. Moreover, as we have indicated, the progressive increase of the carbon deposit, in the lung of every citizen in manufacturing communities, can be recognized and grouped into the age periods by decades, when the individual has lived fairly constantly in the same district. Individuals of similar occupation are expodes to relatively equal amounts of atmospheric carbon, and their respiratory tissues receive similar quantities of carbon by inhalation. On the other hand, in communities where within short ranges of distance the atmospheric conditions differ, and with this the carbon content of the air is very unequal, the people living or working but short distances apart are subjected to diverse conditions, the one inhaling much larger quantities of soot than the other.

There are so many factors associated with the deposit of soot in the lungs of human individuals that it is impossible to make any general statement

indicating the amounts for each. In truth, it is plain that those in smoky atmospheres have larger deposits, but we are often misled in our reference as to occupational unfluence. The millworker employed within the sheds in the manufacture of steel is often less exposed than his wife living within a quarter-mile range enveloped by the smoke clouds from the multitudinous stacks. The lungs of a peddler selling his wares to the foreign population of our smoke-laden valleys were found to contain more carbon than those of the millhand (see table, page 914).

As we feel convinced, from our observations, that the intestinal route has little or no practical significance for the deposit of carbon in the lungs, it does not appear that the degree of cleanliness, particularly of the mouth, bears any relation to pulmonary anthracosis. Carbon particles once lodging upon the moist surfaces of the nose, mouth, pharynx, and trachea, never assist in increasing the carbon of the lung. It is probable, as was shown by Haythorn's experiments, that only those carbon particles lying within the alveolar sacs can reach a permanent interstitial abode and that little if any carbon is phagocyted and carried into the tissues from the bronchi or bronchioles. Furthermore, it would appear, both from experimental and other observations, that the carbon reaching the lung alveoli is only a very small portion of the carbon content of the air as inspired, and this portion has reached the lung because it escaped contact with the moist mucous surfaces of the respiratory tract. Under the most trying circumstances of a smoky atmosphere we are amply protected by the sticky surfaces of tortuous tubes.

Difficult as it seems for carbon to reach the lungs, it appears equally difficult to dislodge the pigment when once it has been incorporated by the tissues. In fact, we may well believe that save under very abnormal circumstances, carbon once within lung tissue remains for life, and hence each year we add that amount to our store as we may have been exposed to city smokes. To gain some accurate information of the quantitative deposit of carbon in the lungs an analysis was made of the tissues. Previous analyses have been made determining the quantity of iron, silicate, copper, and other metallic deposits in the lungs of laborers.

Saito, in a series of experiments, estimated the quantity of dust inhaled from the air. Using measured quantities of dust (white lead), he determined the quantity taken up by the animal when exposed to the dust-laden air. He observed that only 4 to 24 per cent. of dust entering the nose was deposited in the respiratory organs, while the remaining quantity found its way to the intestine.

More recently Boer has made a relative quantitative estimation of the soot content of small portions of lung tissue. By his method, using only three cubic centimeters of lung tissue errors of calculation may possibly be great. He points out the error which would be obtained in comparing

lung tissue of unequal density or consistence, as for example that of emphysema or œdema, and confined his examination to normal lung tissue. Here too much variation may be encountered, whether or not much pigmented pleura is included in the portion under examination. Care in selection of the tissue can not wholly rule out errors of seroius import in the results. Furthermore, as the amount of carbon in these small portions of tissue was too small to weigh, he has used a colorimetric method suggested by Liefmann. The amount of carbon isolated from the lung examples was suspended in a mixture of oil and ether, and compared with a set of standard suspensions, prepared by suspending weighed quantities of nephthalin soot in the same vehicle. Such a colorimetric method cannot be relied upon, owing to the difference in the nature of the carbon in the lungs and naphthalin soot. Fresh soot has physical and chemical properties widely different from the carbon isolated from the lung by treatment with antiformin and alcohol. Isolated carbon from lungs has lost its flakiness and is quite granular, devoid of its phenols and acids. Its bulk is much less than the original soot from which it was derived, and in suspensions taken weight for weight it does not compare with the apparent mass of soot. It is, furthermore, to be noted that in isolating the lung carbon, care must be taken to free the final product of its fat and foreign calcareous matter which tends to remain incorporated in the residue.

In our determinations we took an entire lung, dissected the glands, large bronchi and adventitious tissue at the hilus, and minced the entire organ in a meat machine. The pulp was then divided among four half-liter flasks and to each was added enough of a 75 per cent. solution of antiformin to well fill the flask. The flasks were placed in the incubator and repeatedly shaken for four to six days. Two hundred cubic centimeters of alcohol were then added to each flask and the mixture centrifugalized, the residue being collected and returned to clean flasks. These materials were again subject to fresh digestion with antiformin for a period of four days, recollected, washed and for a third time acted upon by antiformin. After again collecting the residue and washing it, it was treated with 10 per cent. hydrochloric acid, repeatedly agitated and allowed to remain in contact for forty-eight hours. The residue now collected by the centrifuge and washed was in turn treated with acid-alcohol and ether until the supernatent fluid showed no evidence of fat. The ether suspension was then allowed to evaporate to dryness, and the collected residue repeatedly washed with distilled water to rid it of any contained salts. The final product consisted of a pure black, fine powder, denser than the light, fluffy soot masses found in the air. Under the microscope, angular carbon particles were alone present.

Case.	Age.	Occupation.	Residence.	Side.	Quantity of Carbon.
218	22	Laborer	Pittsburgh	Right	3.2
73	28	Peddler	Pittsburgh	Left	5.3
154	37	Laborer	Pittsburgh (6 yrs.)	Right	1.7
163	37	Housekeeper	Pittsburgh	Right	2.1
158	39	Clerk	Pittsburgh	Left	1.2
164	44	Housekeeper	Pittsburgh	Right	2.6
A–Q–8	47	Storekeeper	Ann Arbor	Right	0.145
A–Q–12	68	Laborer	Ann Arbor	Right	0.405
239	69	Carpenter	Pittsburgh	Right	2.81

I am indebted to Prof. A. S. Warthin for the material from Ann Arbor.

In our examination it is shown that the lungs of adult individuals resident in the Pittsburgh district have materially more carbon deposit than the lungs of the two individuals resident in a lesser manufacturing community. Our number for comparison is very small, but is, nevertheless, suggestive of community characteristics. On account of the slow and rather tedious process in isolating the carbon in a pure form, only one lung was examined in each case, so that the total pulmonary content is about double that indicated in the table. Furthermore, it is to be noted that the isolation of the carbon did not include that present in the peribronchial glands, where dense deposits are commonly found.

As was previously indicated, the lungs showing marked anthracosis are decidedly heavier than normal organs, but it must not be inferred that the extra weight is due to the foreign dust in the lungs. From our analysis of the carbon pigment in the lung it is evident that no material increase in weight is obtained directly from this source. On the other hand, it is well shown that a relatively small quantity of carbon in the lung can induce massive fibroid changes which alter the architecture and increase the bulk.

Summary.

Pulmonary anthracosis (not in coal miners) is distinctly an urban disease, and is proportionate to the smoke content of the air.

The soot is inspired and lodges in the pulmonary alveoli, from which it is carried by phagocytes into the lung tissue to become lodged in some portion of the pulmonary lymphatic system.

Although small quantities of carbon deposit in the lung may remain without harm, yet the quantity accumulating in the dweller of the larger cities has an accompanying greater or less fibrosis impairing the elasticity as well as altering the functional capacity of the organ.

The distribution of carbon is fairly uniform in the parenchyma of the different lobes, but there is a considerable variation in the distribution of the pleural deposit. The interlobar and diaphragmatic pleural surfaces show the least pigment. Moreover, less pigment is found in the grooves produced by the ribs or abnormal bands.

Carbon tends to accumulate at the nodal points of junction of the lymphatic channels. The cellular migration of carbon may lead to unusual accumulations in certain areas particularly well demonstrated in the deposit about chronic tuberculous lesions.

Carbon deposits by inducing fibrosis tend to encapsulate chronic tuberculous foci.

Pulmonary anthracosis by itself does not appear to stimulate the production of pleural adhesions.

The actual amount of carbon present in the lungs of different individuals varies considerably and is dependent, in part at least, on the age, occupation, residence and ondition of the lungs (emphysema, collapse, tuberculosis).

I am much indebted to Miss May E. Bothwell for the drawings and for assistance during the progress of the work.

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THE TRIPLE ALLIANCE: HEART, KIDNEY, AND ARTERIAL DISEASE*

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THE simultaneous presence of chronic heart, kidney, and arterial disease is not so uncommon in individuals above middle age. It does not make its appearance in the same characters in the different cases, but when more closely analyzed clinically or studied pathologically, we find similar earmarks of disease in each of the three organs. At times the condition of the heart, at others the finding of Bright's disease, or it may be the sudden development of cerebral conditions, calls our attention to the particular system, suffering the greatest strain, and we are apt, erroneously, to refer to that organ as the sole region of disease. These combinations of heart, kidney, and arterial disease, or any two of them, are most commonly brought to our attention when the process, from a pathological point of view, has become chronic. In no way do we face an acute lesion of an organ, but only the manifestations of a process insidiously progressive, and clinically recognizable late in its development. A correlation of the many facts bearing upon the condition which I have termed the triple alliance, is, I believe, possible.

A physiological alliance has been recognized as existing between the heart, arteries, and the kidneys. The proper function of each is, to some extent, dependent upon the healthy activities of the others. The relationship is perhaps more prominently brought out in the dependence of the function of the kidney as related to the

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heart, while a similar relationship also exists between the heart and the circulation in the arteries. To a great extent this relationship centres around the question of blood pressure within the arteries. It is realized, too, that this blood pressure is normally altered with great ease and that the alteration is observed by a greater or less response in all of these organs. From the recognition of the physiological interdependence of the activities of this group, have proceeded the theories that many of the pathological processes arising in any one, have their explanation in changes occurring in one or both of the other organs.

The lesions which we recognize in heart, kidney, and arterial disease, are of the character of sclerosis in each. The heart is hypertrophied, mainly in its left ventricle, and shows areas of scleroses throughout its musculature. The arteries are thickened with more or less distortion of their lumina, although the altered calibre may not be referable to intimal sclerosis. The kidneys are small and fibrosed, showing characters that we readily classify as chronic interstitial nephritis. In the fully developed cases of heart, kidney, and arterial disease, the fibroses of these organs are marked, though the relative extent of the cirrhotic change differs in each case, sometimes being most marked in the heart, at other times showing an unusual arterial sclerosis or, again, having marked chronic interstitial reactions in the kidneys. Because of the variation in the quantitative deposition of fibrous tissue there has been much speculation in suggesting the disease or the organ which was primarily at fault.

Bright and subsequent pathologists recognized the association of the contracted kidney with morbid changes in other parts of the body, particularly in the presence of hypertrophy of the heart. It was generally believed that the kidney was the organ primarily affected and that other bodily conditions were secondary.

The hypertrophy of the heart has been explained on a purely mechanical basis as due to the difficulty of the circulation in the cirrhotic kidneys. Ewald and, later, Loeb have suggested that the heart lesions were the result of increased work brought about by the greater viscosity of the blood. Others (Hasenfeld and Hirsch) have found that the cardiac hypertrophy was associated particularly with a sclerosis of the splanchnic vessels while scleroses in the remaining portion of the peripheral tree, they believed, had less effect.

In the belief that the kidney was primarily involved in disease and was followed by the retention of a variety of products of meta-

bolism, it was held by some that both the heart and arterial lesions were the result of a chemical irritation. The retained substances, it was claimed, had a direct effect upon the musculature of the heart as well as upon the arteries. It was also suggested that besides this the direct toxic effect of the retained excretions caused a persistent high blood pressure induced by arterial spasm. More recently it has been suggested that chronic kidney disease is accomplished by an abnormal function of the adrenal glands, associated with a greater production of adrenalin. This, it is claimed, leads to a tonic spasm, or contraction of the arterial walls, materially raising the blood pressure to which the cardiac hypertrophy is a response. Thus a variety of factors have been suggested as initiating the hypertrophy of the heart secondary to other diseases.

Even under the circumstances where cardiac hypertrophy is recognized clinically, the heart condition may not have reached the final stage of the process. Insufficiency of the myocardium may yet develop, particularly in the presence of a subsequent disease, as myocarditis, or with a progressive sclerosis of the coronary arteries. These changes, however, are rather to be viewed as complications and sequelæ which do not assist in clearing up the nature and process of the primary disease causing the hypertrophy.

Undoubtedly, when a definite sclerosis of the large and small arteries has occurred, the increased resistance rapidly leads to an alteration in the circulation. The maintainance of an equal supply of blood in the peripheral arterioles demands greater activities on the part of the heart, and whether the heart may properly compensate for this increased demand depends, in the individual case, upon the reserve activities of the musculature. An adequate nutrition, using the term in its broadest sense, will permit the myocardium to compensate by hypertrophy. It may be, as suggested by some, that prior to the arteriosclerosis, the heart may show no evidence of enlargement, but it would be going too far to say that in the absence of recognizable hypertrophic changes, the heart had not previously suffered myocardial lesions. It may be, as some have indicated (Hasenfeld, Romberg), that though the heart be damaged by degeneration, the hypertrophy does not arise until the musculature is given the stimulus for growth by suffering undue stretching.

Hirsch examined a series of cases with cardiac hypertrophy and found that where this hypertrophy was associated with arteriosclerosis, the left ventricle was mainly or alone involved. He also observed that when diseases of the lung and pleura had an effect

upon the pulmonary circulation, the hypertrophy of the heart was mainly on the right side. In a third group of cases those having chronic nephritis, a few showed hypertrophy of the left ventricle alone, but the majority showed that the hypertrophy involved both right and left heart, though the increase was greater upon the left side than the right. It was assumed by Stewart that this latter condition arose from an increased peripheral resistance in an increased viscosity of the blood acting primarily upon the arterioles and then upon the left ventricle. It is also indicated that the cardiac hypertrophy without valvular disease, associated with arteriosclerosis, while more especially affecting the left ventricle, is also present in the auricles (Hirsch). These authors claim that no pathological factor other than that mentioned is available for explanation. In his experimental work Stewart has been able to show that a hypertrophy may be induced by the production of aortic insufficiency and is the result of increased work.

The spirit has gone abroad that wherever arteriosclerosis is present in the body, there must be some increase in the blood pressure. Yet, when this is put to test, it is found that there is no uniform relation between them. Sawada found that in only about 12 per cent. of arteriosclerotics was there a heightened pressure. Romberg noted that in some districts arteriosclerosis was unaccompanied by increased pressure while in others it was the common manifestation. He points out, however, that in the latter chronic interstitial nephritis was a complication. Thus he indicated that arteriosclerosis with nephritis and arteriosclerosis without nephritis may occur in unequal proportion among different people.

There are so many factors which appear to influence the development of chronic disease of the heart, kidney, or arteries, that much speculation has been indulged in respecting the importance of each. Richard Bright, who was among the first to give definite recognition to these associated processes, looked upon the kidney disease as the prime causative factor for hypertrophy of heart. These contentions of Bright were opposed by Rayer, who denied the common association of heart and kidney diseases. Even Frerichs opposed Bright's view and claimed that cardiac hypertrophy preceded the nephritis. Up to this time much confusion existed in the classification of Bright's disease and difficulty was expressed in segregating the types, so that a proper comparison could not be made of the relationship of the diseased process to that in other organs. Traube, in 1845, divided Bright's disease into several groups, in one of which he found heart disease was particu-

larly prone to occur. He believed that some cardiac affections could lead to kidney disease, other than infarction, and eventually to chronic changes. Cardiac hypertrophy, he observed, occurred mainly with the contracted kidney and the left ventricle responded most promptly. This exposition by Traube was favourably received and indicated progress in the recognition of a variety of lesions in the kidney. Johnson, in 1852, noted the association of thickened arteries with chronic Bright's disease. The arterial change he viewed as hypertrophy of the media resulting from an impure blood containing urinary excreta. The minute arteries, it was thought, resisted the passage of this abnormal blood and the heart putting forth an increased effort developed a hypertrophy of the left ventricle.

In 1872 Gull and Sutton again attracted attention to the association of cardiac hypertrophy with chronic nephritis and arterial disease. They were, however, insistent that the cardiac condition was not secondary to the disease in the kidney, but resulted from a general arterio-capillary fibrosis. This vascular lesion they believed was not isolated to any part of the body, but was generalized, involving all the small arterioles. The vascular changes were present in the heart muscle as well as the kidney and other parenchymatous organs. It was claimed that this widespread arterial disease bore the same relationship to the interstitial myocarditis, as did the acute softening of the heart muscle to the embolic process of the coronary arteries as described by Virchow. These contentions of Gull and Sutton were substantiated by Buhl, Koester, Huber, Sternberg, and others. The cardiac disease was looked upon as resulting from an altered nutrition consequent to the coronary sclerosis. Previous to these observations much stress has been laid upon so-called idiopathic hypertrophy of the heart.

Gull and Sutton showed that the vascular lesions were independent of renal disease and that the kidney condition was a manifestation of a more general systemic process. Furthermore, they indicated that in other kidney diseases where much destruction of renal substance had taken place, with the probable retention of excreta, no cardiac hypertrophy was found. That cardiac hypertrophy was not the result of renal disease was illustrated in the fact that it might occur without the presence of kidney involvement, as well as preceding chronic Bright's disease. The authors observed a hyaline fibrous change about the vessels of the heart similar to that which they had found in the kidney. This they considered

was, in part at least, the cause of the hypertrophy. Gull and Sutton observed that the arteries in the pia mater in chronic interstitial nephritis sometimes showed a thickening of the intima, sometimes a hypertrophy of the media, but more commonly a fibrosis surrounding the vessel. The media sometimes was atrophied. These same changes were further found in the skin, stomach, spleen, lungs, heart, and kidneys. In a table of ages of patients examined, the authors have found that granular conditions of the kidney belong to a period of life at or over forty years of age. However, in the few cases in which the condition was found before the age of forty, the general disease process simulated those at more advanced ages. Here, too, there was observed the periarterial thickening accompanied by hypertrophy of the heart. They pointed out that clinically the manifestations of this general disease might be such that no attention is attracted to the heart, kidney, or arteries, but only after other progressive changes have damaged one of these systems may we recognize the presence of chronic Bright's disease with its accompanying manifestations. In the early stages the symptoms depending upon the intensity of the vascular involvement may be more evident in diverse parts of the body. In conclusion they recognized a systemic disease of the arterioles and capillaries which, as a periarterial fibrosis, may begin in the kidney, but which also has its pathological changes in other organs.

Our attention must not be too closely centred upon the conditions arising in any one organ. A general perspective of the lesions throughout the body is essential, and for this purpose nothing short of a combined study of many regions will allow us a proper interpretation of the diseased processes in question. It is furthermore necessary to study the disease in its various stages of development. Too much stress has been laid upon the importance of the pathological changes in the heart, kidney, or the arteries after one or other of them has suffered severely. To indicate that the heart and arteries are subject to a sclerosis in chronic interstitial nephritis is simply a statement of the gross pathological features observed in an individual after he has passed through consecutive stages of a disease and arrived at a point where the functional activities of several organs are so impaired that a continuance of healthy life is impossible.

Thus the observations upon the clinical pathology of these associated diseases are far from clearing up the moot points concerning the importance of common processes. Difficulty is experienced in indicating the beginning of a sequence of changes whose

manifestations are not the same, and whose recognition is only late in the progress of those changes. Some of the clinical features have been explained upon pathological findings. But here again much difficulty has been experienced in indicating the order in which the lesions have occurred. Conclusions have been drawn from studies made upon fully developed cases alone. In respect to these, the observers do not differ so much in the recognition of the lesions, but in the importance of each as dominating the presence and progress of others.

Senator points out that while there are a great number of factors which, upon purely theoretical grounds, may be suggested as the causative factor leading to cardiac hypertrophy, it is probable that no single cause may be found to account for all, as the individual conditions differ considerably in each case. Thus he believes that the increased viscosity of the blood, the narrowing of the capillary bed, the thickening of the muscular coat of the arterioles, the resistance of the blood stream displayed by the visceral arteries, as well as other factors, might be important causes for some cases, yet each will not act with equal intensity in the different individuals. He has further observed that the molecular concentration of the blood differs in the different forms of nephritis. The blood contains substances which are toxic for various tissue and the character and concentration of the albumens are altered. These changes have a direct effect on the heart muscle as well as an irritating action on the vessel walls, stimulating them to contraction.

He points out that chronic interstitial nephritis is a slowly progressive disease in which the changes do not occur suddenly. The altered blood content gradually acts upon the vessel walls, leading to histological changes as well as functional incapacity of their tissues. The circulatory change as well as the direct effect of the altered blood upon the heart is, he believes, the main cause for cardiac hypertrophy. He further suggests, however, that it is quite possible for the true causative factor to exist outside of the heart and kidney and to attack these organs simultaneously.

Although fibrous myocarditis was noted by Veniviene (1529) and later discussed by Morgagni, its nature was not appreciated until 1806, when Corvisart recognized it as an inflammatory process and believed that it was always associated with a pericarditis or an endocarditis.

Pathologically the chronic, fibrous myocarditis indicates a replacement of the muscular tissue of the heart by connective tissue. The left ventricle is mostly involved. Commonly when

small patches of fibroses are observed in the heart it is found that they had given no clinical evidence of their presence. It has, however, been demonstrated that the presence of connective tissue greatly interferes with the function of the heart by reducing its elasticity as well as its contractile power. Its association with cardiac hypertrophy has been commented upon, while Rigal and Juhel-Renoy have applied the term *"myocardite-scléreuse hypertrophique,"* to this association. Leyden called attention to the several forms of cardiac sclerosis, sometimes observed in a diffuse and scattered manner while in other individuals isolated plaques are found. Koester drew attention to the frequency of the process and indicated the more important pathological characteristics of the disease. The fibrous areas appear as parallel tendinous streaks following the direction of the muscle cells. The distribution of these areas is not uniform. They are commonly present at the apex while the posterior and upper portion of the left ventricle may also show much involvement. They are prone to lie quite superficially either directly beneath the pericardium or close to the endocardium. The papillary muscles of the left ventricle are also structures showing a predilection for this process. Koester was able to observe that this development of connective tissue in the heart resulted from two different causes, on the one hand associated with inflammation with secondary destruction of the muscle fibres, or otherwise as a degenerative process without inflammatory change and associated with disturbance of the coronary arterioles. The former type is the one which is particularly associated with kidney and arterial disease. The distribution of the lesions in the heart muscle is quite characteristic, and may be observed in different stages of development. Inflammation precedes the development of the connective tissue in all. Koester believed that this myocarditis had its origin in infection, while Ruehle observed that it was most commonly associated with rheumatism. It was likewise pointed out by others that myocarditis as it occurs in rheumatism and its allied diseases was associated with endocarditis and pericarditis.

Aschoff and others have described an acute non-suppurative lesion of the myocardium occurring during an attack of acute rheumatic fever, acute articular rheumatism, muscular rheumatism, and rheumatoid affections. This heart lesion is quite distinctive and differs from that observed in infections by pyogenic organisms as well as by a variety of specific organisms. The lesions in the heart are focal and develop in the vicinity of the nutrient vessels

of the myocardium. Isolated areas of inflammatory exudate surround the small arterioles leading to greater or less degeneration of the musculature in the vicinity. The greatest amount of damage by these foci is produced in the outermost coat of these vessels and in the tissues immediately surrounding them. The small arterioles are in themselves not extensively involved during the acute stage. Gradually, however, as the process enters upon a chronic stage there is a thickening of the vessel wall, partly due to an hypertrophy, but mainly due to a fibrosis occurring in the adventitia with some thickening of the media. The total bulk of heart that is affected by this perivascular inflammation, is considerable, and the myocardial weakening observed in these affections is the result of the degeneration of the heart muscle occurring immediately about the nutrient vessels.

These observations by Aschoff and Tawara were confirmed in experimental studies by Waechter and others. It was shown that when organisms (streptococci) isolated from cases of acute rheumatic fever and the milder allied diseases, were inoculated into susceptible animals, tissue disturbances simulating the original disease in man could be readily induced. Not alone were the clinical manifestations reproduced but lesions occurred in the myocardium of a nature similar to those noted in the human heart. The lesions have been found so characteristic that from the myocardial picture alone the diagnosis of a rheumatic affection could be made. In a series of experiments to which we will refer again we have been able to confirm the findings of Waechter.

In an individual study reported upon during the past year we have made observations upon the various arteries of the body during acute rheumatic fever. It was observed that the larger vessels, and more particularly the arch of the aorta, which are supplied by nutrient vessels advancing into the outer and middle coat, suffered a non-suppurative inflammatory reaction similar to that found in the heart. This reaction was of the same character as that in the myocardium and was disposed in a perivascular manner. The vasa vasorum of the arteries take the place of the small divisions of the coronary arteries of the heart. These vasa vasorum carry the burden of the reaction in the vessel wall. Accompanying the reaction there is a certain destruction of the essential elements of the arterial coat, leaving the vessel weaker and subject to subsequent fibrous replacement of its own tissue. In our earlier studies it appeared to us that the peripheral arteries did not become involved. This conclusion was mainly drawn from a study of arteries

of intermediate size which passed to the limbs and to the main viscera. It is true that in the majority of cases these moderate sized arteries of the muscular type show no evidence of inflammatory invasion. Nevertheless, as we then indicated, an irregular distribution of the inflammatory reaction may be observed in some of the arterioles when the larger visceral arteries are not involved.

In the cases which we have examined, the simultaneous occurrence of lesions in the myocardium and the arteries has been very constant. The intensity of the reaction in each or both has been varied; at times that in the heart being greater and out of proportion to that in the arteries, at other times again, the reverse was observed. Moreover, we have been able to follow the processes during the various stages of development. From the acute non-suppurative variety with extensive perivascular infiltration of the small arterioles all gradations of chronicity with progressive fibrosis have been found. The amount of fibrosis occurring in the vicinity of the arterioles was dependent upon the intensity of the reaction, and the extent to which the neighboring parenchymatous tissue was affected. From the minute, microscopic fibrous tissue masses to the larger fibrous streaks, such as are observed in the heart and large vessels, all degrees and stages were demonstrated.

It is in association with these particular arterial lesions that hypertrophy of the heart is prone to develop. This hypertrophy, however, does not begin to show itself until the reparative processes about the minute vascular channels become evident. In many cases the heart suffers some dilatation of its cavities during the acute stages, but though the heart at this time is receiving the stimulus for growth through stretching, it is unable to compensate so early by hypertrophy on account of the systemic illness, which offers the explanation in an inadequate nutrition. Hypertrophy does not begin until recovery from the effects of the immediate acute involvement has passed over. Repair of the inflammatory focus does not begin until, in part, at least, the infection is overcome. From this time on not alone is there a repair of the lesion induced during the inflammatory reaction, but also opportunity is given for the compensation of the weakened myocardium sustained in muscular degeneration.

When, now, we suggest a type of kidney lesion ending in chronic interstitial nephritis as commonly associated with this combination of acute and subacute myocarditis and arteritis, we will receive considerable opposition from clinical observers. The constancy of association of myocarditis and mesarterial diseases has

gradually impressed itself upon us so that we view this occurrence as the usual lesion in certain forms of infection. We have hardly reached the time when all are willing to place definite forms of kidney disease in the same group. Nevertheless, an examination of human material as well as experimental studies force us to accept this view. As is true with so many forms of non-suppurative infections in which a bacteriæmia is temporarily and periodically present, many of the organs suffer unequally. The bacterial attack upon various tissues is only an incident in the disease, and it would be impossible to designate the lesion in each organ as a common or constant manifestation.

With the type of infection which dominates acute and subacute cardiac disease, we recognize organisms which are not constant in their virulence, which are sporadic in their systemic distribution and which are very uncertain in their localization in the tissues of the body. At times, during a given illness a dissemination of bacteria occurs in the blood stream for short periods of time, then the circulation is rapidly freed from the meteor-like distribution, only to be involved in a subsequent and similar reinfection from a local focus. The disease does not carry with it a constant bacteriæmia.

As, then, the hæmatogenic infection of different organs is so uncertain and unequal, the lesions arising in different cases are difficult of comparison. We have, however, found that inflammatory changes arising in the interstitial tissue of the kidney were not so uncommon in these infections. In the milder forms where the kidney was least involved and where clinical evidence of a nephritis was wanting, the lesion consisted of a lymphocytic and plasma cell infiltration in the interstitial tissue close to the interlobular arterioles. This subacute inflammatory reaction was distributed mainly about the arterioles and began in about the middle of the medulla. The inner coats of these arteries were not appreciably altered but the adventitia was quite loose and œdematous with an infiltration of lymphocytes. From the perivascular lesion the inflammatory exudate spread along the course of the vessel into the cortex, so that streaks of infiltration could be followed from the medulla to the surface of the organ. Primarily, this perivascular non-suppurative inflammation with its œdema gave a more bulky appearance to the involved areas. The tubules of the vicinity were surrounded by the exudate of cells while but little change occurred in the epithelial lining. Similarly, the capsules of the neighbouring glomeruli were not uncommonly surrounded by a similar infiltration.

For the most part the inflammatory reaction was present in radiating zones, leaving intervening patches of kidney tissue uninvolved. The larger vessels near the base of the pyramids also showed a perivascular reaction, but the main artery to the kidney was, in itself, devoid of inflammatory change.

This non-suppurative inflammatory reaction beginning in the vicinity of the interlobular vessels and extending through the cortex appears to be a typical lesion associated with the common subacute inflammation of the myocardium. In the human organs, however, it is usually associated with other lesions which tend to obliterate the character here described. Individuals dying during the first attack of acute infective myocarditial disease have commonly extensive endocardial vegetations. The presence of embolic masses of small or large size is apt to involve the kidney in a well marked infarct or lead to the occlusion of the vessels to the glomeruli with subsequent changes in these structures, not definitely to be viewed as the typical lesion of the disease.

We must, however, recognize a form of acute glomerulonephritis with the local exudate, and occasionally showing a proliferative reaction within the glomerulus or its capsule, as a common reaction of the kidney. The presence of an acute glomerulonephritis in a number of bacterial diseases is now well recognized, particularly through the work of Councilman and Loehlein.

The observations upon the various types of acute non-suppurative nephritis, indicate the close relation of the lesion to the circulatory apparatus. That at times the lesion is greater in the glomerulus while at others the perivascular reaction appears more intense, is not to be wondered at, when we remember the unequal reaction in tissues by many varieties of bacteria. Moreover, the different forms of reaction occurring within the glomeruli may well be variations in the intensity of reaction to a single strain of organism. Thus, as has been amply illustrated in late years, a single irritating agent such as uranium nitrate may give rise to tubular, glomerular, and even vascular lesions in the kidney. We have repeatedly observed a variety of pathological processes in different glomeruli brought about by the same bacterial agent.

These inflammatory disturbances of the kidney, showing their main reaction about the blood vessels and their associated parts, were observed in the early stages of heart and arterial disease. When closely analyzed it will be observed that the reaction in each of these tissues, heart, kidney, and arteries is very similar. There is a type of subacute inflammation particularly distributed in the

vicinity of the small nutrient vessels, disturbing the parenchymatous tissue in the immediate vicinity. We have indicated the late effect of this inflammation upon the heart muscle as well as the disturbance of the media of the arteries. We now call attention to the effect of the inflammatory reaction upon kidney tissue.

In the milder conditions the reaction remains localized in the vicinity of the vessels, causing but little disturbance of the tubules or glomeruli. An œdema pervades the intertubular connective tissue in the interlobular zone. Relatively little kidney tissue is involved by this localized inflammation, although streaks of reaction follow many of the small cortical arterioles. Where the reaction is more intense the infiltration spreads for some distance into the cortex involving considerable areas in an irritative process. More or less tubular degeneration may be present and granular debris appears within the secreting structures. The glomeruli may be involved in congestion with proliferation or show the presence of a lymphocytic infiltration amidst the capillary loops. Some of the glomeruli may become occluded and undergo hyaline change. Crescentic spaces between the glomerulus and its capsule show the presence of debris and hyaline masses. Occasionally hyaline and granular casts are found within the tubules.

As these inflammatory lesions progress to the chronic stages, the perivascular areas of infiltration become replaced by connective tissue. There appears to be a large gap in the observations, both clinical and pathological, between the acute and chronic stages of the disease. Many individuals die during the height of the disease when the acute reaction is well evident in the kidney. Otherwise death does not overtake them, save through intercurrent accident, until the late sequelæ bring about these changes in the heart, kidneys, or arteries, which have been so thoroughly observed and studied. The intermediate stages of repair are infrequently seen. Nevertheless, one may observe combinations of the acute and chronic lesions in those cases where the disease has been of a recurrent nature. This is not so uncommon, and we have observed a number of instances where perivascular fibrosis was accompanied by an acute lymphocytic infiltration. The acute lesions of the heart were a further evidence that the inflammatory infiltration was a recurrent one and not that of a progressive disease.

The healing of the acute inflammatory exudate takes place by a fibrosis which is observed in radiating streaks advancing from the base of the pyramids through the cortex. The small arterioles which ramify from the interlobular vessels carry with them an

excess of connective tissue. This fibrosis develops through the
increase of connective tissue around the small vessels and becomes
attached to the fibrous capsule of the organ. The radiating char-
acter of this fibrosis is quite distinct. Only secondarily does it
involve the tubules and glomeruli which lie in its path in the cortex.
The structures intervening between these lines of fibrosis are un-
involved in the cirrhotic change so that many glomeruli throughout
the cortex have normal characters and the tubules lying outside
of the zone of fibrosis are unchanged. With the shrinkage which
accompanies all forms of inflammatory fibrosis, the involved areas
tend to narrow the cortex by drawing the surface closer to the outer
border of the medulla. The unequal distribution of the fibrous
tissue leads to an irregular amount of contraction producing a very
granular kidney. Naturally the amount of shrinkage is dependent
upon the state of the disease as well as the intensity of the primary
inflammatory process. This final stage is known to us as the
granular kidney, the genuine contracted kidney, or true chronic
interstitial nephritis.

In our discussion we have suggested a bacterial irritant under-
lying the inflammatory reactions in each of the involved organs.
The same organism appears capable of producing inflammatory
lesions simultaneously in many tissues and owes its distribution
to the blood stream.

In recent years much has been done to indicate the import-
ance of definite streptococcal infections in the inflammatory lesions
of the heart and circulatory organs. Although all are not agreed
upon the particular type of organism which is mainly at fault, yet
it is important that various observers have had their attention
attracted to an organism or group of organisms which induce a sub-
infection, having more severe focal processes in one or other organ.
Though we believe that these focal depositions of bacterial infection
may involve many different organs and bring about various grades
of inflammatory reaction, our chief attention has centred about
the infective heart disease. Nevertheless, the arteries, meninges,
kidneys, joints, and liver have been shown to be variously involved
in different cases. A study of the organisms associated with such
lesions has called forth a nomenclature greatly confusing the sub-
ject.

The important bacteria belong to the group of streptococci,
and may be recognized by their biological characters and separated
from the pus-producing streptococcus, as well as from the pneu-
mococcus. By Schottmuller this variety of streptococcus was

named the streptococcus viridans. In the further investigations it was shown that streptococcus viridans represented a group of organisms which, although having some common characteristics separating them from other members of the streptococcus group, had further points of differentiation which divided the group into a number of types, whose characteristics were fixed and whose habitat was more or less defined. To this group belong the streptococcus fecalis, streptococcus salivarius, streptococcus equinus, streptococcus mitis, and several unnamed forms. The group in itself is quite distinct and by proper means can be readily recognized.

The organisms which have been isolated by different observers from acute and subacute endocarditis belong to the streptococcus viridans group as described by Schottmuller. Such organisms as were described by Poynton and Paine as the streptococcus rheumaticus, the endocarditis coccus of Libman, and the organisms described by Rosenow must be considered as members of this group. It has been pointed out by Gordon and others, including my colleague, Dr. Holman, that the organisms found in connexion with heart lesions do not represent an individual type or a specific variety, but recognizing that they belong to the streptococcus viridans group, they may be represented in a variety of types. Of five organisms obtained from different cases of heart disease, three were shown by Gordon to simulate the streptococcus mitis, while two had characters similar to streptococcus salivarius. Dr. Holman has likewise demonstrated the type of streptococcus salivarius in the blood of patients with vegetative endocarditis, while in three other instances he isolated a form simulating the streptococcus fecalis and in another the streptococcus equinus. Andrewes and Horder in an extensive study upon streptococci found the presence of the streptococcus viridans in fifteen out of twenty-three cases of malignant endocarditis. Of these, eleven belong to the group of streptococcus salivarius; and four to streptococcus fecalis.

In five of our cases having acute non-suppurative processes in the heart, arteries, and kidneys, there was isolated a type of the streptococcus viridans from the blood at autopsy.

The association of these organisms with the occurrence of inflammatory processes in each of the three organs under discussion, led us to test our results upon animals. Through the kindness of Dr. Holman, I had the opportunity of obtaining a number of types of the streptococcus viridans for the tests. Rabbits were used, and living cultures in different amounts were inoculated intravenously. Nine cultures giving the reaction of the streptococcus fecalis,

seven streptococcus mitis, four streptococcus salivarius, one streptococcus equinus, and four other unnamed types of the streptococcus viridans were used. None of these inoculations gave rise to pus formation (one recently isolated strain of streptococcus salivarius was found to be highly virulent for rabbits, death being produced in forty-eight to seventy-two hours). The inoculated animals were killed at different intervals, and the lesions were studied both macroscopically and microscopically. In the majority of instances only one inoculation was given.

In brief, we were able to demonstrate pathological processes in the majority of animals surviving beyond the forth day. The variation in the pathogenicity was quite evident even among the organisms of the same strain. Some of the older cultures proved to be of low pathogenicity so that, although a slight non-suppurative reaction appeared at the end of the first week, complete resolution occurred within a month. On the other hand, the more virulent forms showed quite intense reactions by the end of the first week which persisted for varying periods of time up to six weeks. When, however, the inoculations were repeated at intervals of three weeks, a progressive inflammation with productive fibrosis was observed over a period of seven months.

In our experiments we were unable to indicate definitely the type of organism which appeared to give the greatest tissue reaction. The variation in the length of time in which the different organisms had been cultivated on artificial media had greatly altered their pathogenic qualities.

The particular point, however, in which we were interested was the simultaneous occurrence of lesions in the heart, arteries, and kidney. The affection of the heart was mainly to be observed in the myocarditis which simulated that described for the human heart. An interstitial infiltration of lymphocytes and plasma cells was the usual observation, and this infiltration was mainly in the vicinity of the small arteries. We failed to demonstrate the uniform periarteritis and mesarteritis of the ascending aorta, as we have on a previous occasion indicated for the human vessel. In two instances a slight grade of periaortitis was present. Otherwise, however, we found an irregular and inconstant periarteritis of the arteries of the liver, diaphragm, mesentery, and kidney. In the latter organ upon which our attention was concentrated, some remarkable results were obtained.

The kidney lesions were common and occurred in greater frequency and intensity than in the heart. They were associated

with the vascular system of the organ. The larger vessels were the least involved, but the interlobular vessels and the afferrent vessels of the glomeruli showed an inflammatory attack of a considerable degree. The nature of distribution of these vessels led to a radiating character of the inflammatory process, extending from the intermediate zone to the capsule. The picture was identical with that described in the spontaneous lesions in man. Moreover, all gradations from the acute process to the chronic fibrosis could be followed. A mild grade of granular kidney was produced. In three instances in which the disease had lasted over four months there appeared slight hypertrophy of the heart.

For the present I need not go into the further details of these experiments, save to indicate that the lesions produced experimentally closely resembled those which we meet with clinically. The important finding of the correlation of the heart and kidney in the inflammatory reactions, is worthy of comment to indicate how a general bacterial process may underly a pathological condition arising in each, and before either of these organs has an affect upon the other through its functional incapacity. The cardiac degeneration occurs during the early and acute stages of the disease. The repair with its accompanying fibrosis is prone to have hypertrophy develop with it. So too, the kidney lesion is individual, developing from a bacterial irritant inducing fibrosis about its blood vessels. A vicious circle may, no doubt, develop in the course of the disease which may react on other vital organs. The peculiarity of the infection in being distributed by the small arterioles and having its main action upon the tissue in the vicinity of these, is worthy of our notice. This finding is but a substantiation of the observations of Gull and Sutton. It appears, therefore, that the heart and kidneys bear to each other a relation during this infection only in proportion to the nature and distribution of the inflammation about their vascular system.

I would not have you believe that the arterial affection as an arteriosclerosis is the predominant one, but the organic changes are dependent upon the distribution and the extent of the perivascular inflammatory attack. Moreover, I further wish to indicate that the interdependence of the lesions of the heart and kidneys is through their circulatory system, but not because of an arteriosclerosis as we ordinarily understand it.

Thus our "triple alliance" is complete. Each of the three organs has its individual duty to perform, which has an important bearing upon the health of the other. Common enemies (bacteria)

attack them simultaneously, leaving one, or another, or all, badly abused. Repair of the injuries results in fibrosis which may manifest itself in the "senile syndrome."

The hypertrophy of the heart has its beginning in a process of repair of the heart muscle damaged by bacterial invasion. Subsequent factors, such as increase of the blood pressure and the effect of retained excretory products, probably assist in increasing the cardiac hypertrophy in the later stages of the disease.

The typical arterial lesions under discussion are not what is ordinarily classified as an arteriosclerosis, but consist mainly in a periarterial reaction. Just what relation there may be between the periarterial inflammation of this type and modular intimal arteriosclerosis, we are at present unable to say. However, this is evident from our observations, that the periarterial inflammation following the vasa vasorum precedes the reaction in the intima. The late manifestations of the arterial involvement are observed in a perivascular fibrosis.

The kidney lesions are of the nature of a true non-suppurative interstitial inflammation which begins in the perivascular tissues. The inflammatory reaction follows the distribution of the arterial supply, involving also the glomeruli to a greater or less degree. The chronic stage follows with repair by fibrous tissue, and subsequent contraction of the organ leads to the small granular kidney. Tubular changes are not great and are secondary.

74 (891)

Liver necroses associated with Streptococcus infection.

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In a series of experiments upon rabbits to determine the tissue reactions to the infection by the *Streptococcus viridans* and having special reference to the heart, arteries, and kidneys, several sporadic examples of necrosis of the liver were encountered. Living cultures of *Streptococcus fecalis*, *Streptococcus mitis*, and *Streptococcus salivarius* were used. Repeated inoculations, from three to five, had been made at intervals of four days.

The earliest necroses appeared in eleven days and consisted of small focal areas in the peripheral and mid-zones of the liver lobules. In them only a few cells appeared to be affected and seemed to be sporadically picked out in the midst of the liver column. Debris or the ghosts of cells, was all that remained. There appeared to be some edema in the involved area but evidence of thrombosis in the neighboring sinuses was not always demonstrable. In some instances a granular thrombus with fibrin threads was present immediately about the lesion, and at times, extended towards the central vein. Similar thrombi, however, were also observed in areas not showing necrosis.

Some liver columns appeared to show change antecedent to necrosis. In them the cells showed a diminution of nuclear staining with an eosinophile character of the protoplasm. In the vicinity of these again, thromboses were wanting.

Other areas again showed much more advanced necrosis involving not only focal areas but entire lobules or even several neighboring lobules. In all of these instances the necrosis involved the central and mid-zone, while some liver columns still persisted in the vicinity of the portal sheath. In these larger areas thromboses

of the mixed fibrinous variety were common. The sinuses of the affected areas were irregularly involved, but not constantly, the central vein being most commonly plugged. These thromboses extended into the sub-lobular vein. Thrombi of agglutinated red blood cells were not observed. There was no inflammatory reaction in the large areas of necrosis nor was there any attempt at restitution either by connective tissue or liver cells.

In 1906, Pease and Pearce[1] noted the occurrence of liver necroses in horses, immunized against the streptococcus pyogenes. In their cases the liver showed diffuse necrosis but they were unable to demonstrate the nature of the process. Since then much literature has appeared in the discussion of liver necroses, and the condition has been described in a great variety of intoxications.

In the absence of thrombi and a cellular reaction in many of the early necroses observed in our cases, it would appear that they have resulted by a direct intoxication by these streptococci. The mixed fibrinous thrombi, developing in the blood channels distal to the liver involvement, probably result from ferments liberated from the damaged liver cells. Such progressive thrombosis assists in producing a more widespread necrosis of the partly damaged liver tissue, even involving several neighboring lobules.

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[1] *Jour. Inf. Diseases*, 1906, III, p. 619.

THE USE OF DECOLORIZED ACID FUCHSIN AS AN ACID INDICATOR IN CARBOHYDRATE FERMENTATION TESTS WITH SOME REMARKS ON ACID PRODUCTION BY BACTERIA

W. L. HOLMAN

THE USE OF DECOLORIZED ACID FUCHSIN AS AN ACID INDICATOR IN CARBOHYDRATE FERMENTATION TESTS WITH SOME REMARKS ON ACID PRODUCTION BY BACTERIA

W. L. HOLMAN

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In 1895 Andrade-Penny[1] reported his results on the use of "acid fuchsin for the differentiation of bacteria." This author employed an aqueous solution of acid fuchsin (fuchsin S. Grubler) and found it to be an excellent indicator for acids and alkalies. When added to various glycerin media it served to demonstrate the reactions which resulted from the growth and activity of certain of the intestinal bacteria.

In 1906, Andrade[2] carried the work further, and he strongly advocated the use of glycerin, Dunham's solution, with the acid fuchsin indicator for the differentiation of the bacillus typhosus. For some time our laboratory was employing this medium as a routine for the purpose suggested, and it occurred to us that the indicator could be extended to the other carbohydrates used in our fermentation tests. I therefore added it to various carbohydrate media, and the results proved it to be a very useful addition to our bacteriological technic. I have found it eminently satisfactory as an indicator of the production of acid resulting from the fermentation of carbohydrates by bacteria, and realizing that it is employed in very few bacteriological laboratories, I feel that its use should be more widely extended.

The indicator is prepared as follows:

Acid fuchsin (fuchsin S. Grubler).....................0.5 gm.
Distilled water ....100 c.c.

To this solution, which is of rich magenta color, normal sodium hydrate is added until the color is changed to pink, then to a brownish red and this, in turn, is changed to yellow. The change of color takes place slowly, and the solution must be thoroughly shaken after each addition of the alkali. Andrade remarked that a pale pink solution

1. *Ann. Rep. U. S. M.-H. S.,* 1895, p. 385.
2. *Jour. Med. Research,* 1906, 14, p. 551.

will become yellow after standing for an hour or two. It is most practical to add the normal sodium hydrate until a definite yellow color is obtained. It usually takes about 17 c.c. normal soda solution to completely decolorize 100 c.c. of the 0.5 per cent. fuchsin solution. One c.c. of this indicator is added to 100 c.c. of the carbohydrate medium.

I have found that broth made + 0.6 to phenolphthalein (hot titration) remains colorless on the addition of the fuchsin indicator prepared as described above. During sterilization at 100 C. the broth turns a distinct pink. This color disappears on cooling, and the medium remains colorless at room and incubator temperature.

Undoubtedly the acid in the broth is partially neutralized by the addition of the indicator, as the final broth is found to be neutral to phenolphthalein in the cold. I have found as has Winslow[3] and others that the use of phenolphthalein at 100 C. shows slightly higher acid reaction than when used in the cold. This gives a double control on a neutral point for the broth; a slight reaction in the cold to phenolphthalein but not to the fuchsin indicator, and at 100 C. a slight acid reaction to the fuchsin but none to phenolphthalein.

The indicator is made up in large quantities. It should be tested twenty-four hours after the last addition of the alkali by adding it to + 0.6 broth in 1 per cent. quantities. A pink color appears on boiling and this on cooling fades, leaving the broth unchanged in color.

This indicator is very sensitive to the presence of the organic and mineral acids. One thousand c.c. of water containing 1 drop of concentrated lactic acid, butyric acid, acetic acid, or tannic acid (20 per cent. solution) turns pink on the addition of the indicator.

During the fermentation of the various carbohydrates by bacterial growth, organic acids (most frequently lactic acid) are produced, any one of which, acting on the fuchsin salt, sets free the fuchsin, and turns our media pink or red. The depth of the color depends roughly on the amount of acid produced.

The fuchsin salt is very stable. It is not affected by heating to 100 C. and over, and no dissociation takes place after the indicator has remained for years in the media. It has no appreciable effect on the growth of even the most sensitive organisms.

Mereshkowsky[4] says that fuchsin in a dilution of 1-1,000 delays, to some extent, the action of invertase, and occasionally renders it

3. Systematic Relationships of the Coccaceae, New York, 1908.
4. Quoted by Fuhrmann, Bakterienenzyme, Jena, 1907.

inactive. The fuchsin, as used in the Andrade indicator, is in a dilution of over 1-20,000 and in our experience has no demonstrable effect in checking or delaying the action of this ferment in the fermentation of saccharose. I have made a number of comparisons to definitely determine this point, using azolitmin and Andrade's fuchsin as indicators. A quantity of saccharose broth was divided into equal parts, the two indicators added, tubed in Durham's fermentation tubes, and sterilized together. A number of strains of the bacilli proteus, clocae, coli communior, lactis aërogenes, acidi lactici, xerosis, together with yeast were used to seed the medium. The results showed: (1) that acid was indicated earlier in the tubes containing Andrade's indicator; (2) that no acid was shown by either indicator in the tubes seeded with non-saccharose fermenting bacteria; (3) that the amount of gas formed by the acid and gas fermenters was the same; and (4) that the litmus was rapidly decolorized by many of the strains making the reading for acid difficult or impossible. From these results and experience extending over several years, I conclude that Andrade's indicator has decided advantages over litmus or azolitmin in that: the indication of the presence of acid is clear-cut and definite; the cultures may be examined and the reading made as well by artificial light as by daylight; it is unnecessary to make comparisons with a control tube; as our media in the neutral state is colorless, there is not the difficulty of making every batch of media exactly the same shade of violet as with litmus; litmus is also much more easily decolorized by reduction, which adds to the difficulty of determining acid production.

For teaching purposes and for use by the student, Andrade's indicator fills a long-felt want.

The method of titrating with phenolphthalein, in order to obtain the exact percentage of acid produced after different periods of growth, is too cumbersome for routine laboratory work and offers little or no help in the diagnosing of our cultures. In the differentiation of bovine from human strains of the bacillus tuberculosis, however, the titration determinations are of great importance as first shown by Theobald Smith. There are, however, too many variable factors to be considered to make it of practical use excepting in these very special biological researches. The number of organisms transferred, the age of the culture used for the planting, and the late previous environment of the strain, all lead to wide differences in the exact percentage of acid pro-

duced in a given time by one and the same organism. It is often
difficult, when one makes transfers of one organism to a number of
different tubes or flasks of even the same lot of medium, to obtain
the same titration results from the whole series. Working with dif-
ferent lots of media, however carefully made, the difficulty of obtain-
ing identical results is increased.

Andrade's indicator is useful in making titration determinations of
the acid produced, where this is particularly desired. Measured quan-
tities of alkali are added to known amounts of media in test tubes or
flasks until the pink color disappears. Precaution must be taken to
allow sufficient time for the adjustment between the acid and alkali
to take place.

The presence of slight amounts of alkali in carbohydrate media
does not interfere with the indication of acid production as so many
investigators seem to believe. Unless the alkali is present in such
quantities as actually to prevent the growth of the organisms, the acid
soon neutralizes the alkali and growth and fermentation continues
until the acid produced is sufficient to either kill the bacteria or to
interfere with their specific biological functions. Winslow in a study
of thirty-three strains of cocci concludes that an excess of acid over
1 per cent. is more generally fatal than an alkaline reaction. The pres-
ence of acid in media has a very detrimental effect on the life of many
bacteria, such as the cholera vibrio, certain streptococci, and many
others.[5] The addition of carbohydrates to media increases the growth
of bacteria, which have the power to ferment the particular carbo-
hydrate, but lessens the longevity of the organisms.

The acid produced in fermentation first affects the biological func-
tion of producing ferments, or lessens the action of such ferments if
produced, and then the acid gradually kills the bacteria. It is true,
however, that very rarely ferments have been known to outlive the
bacteria.[6] Fuhrmann[7] refers to the large number of bacteria which
break up the simple sugars to lactic acid, and says that these bacteria
are very sensitive to the action of acids, especially lactic acid, which
checks their growth and activity.

The fermentation of a given carbohydrate by an organism is a
definite biological character of that organism. The acid death point
is a question of vital resistance. The acid point at which bacterial

5. Lafar, Handb. d. Tech. Mykol., Jena, 1907; *Am. Jour. Pub. Health,* 1913, 3, p. 1210.
6. Lafar, Handb. d. Tech. Mykol., Jena, 1907.
7. Bakterienenzyme, Jena, 1907.

functions cease is a question of biological functional resistance. I have shown that by adding sterile sodium hydrate solution (N/20) to dextrose broth cultures of streptococci each day, to prevent the accumulation of acid, the total acid produced is increased three to four times over that in the unneutralized controls. Similar methods were used by Fischer[8] in determining the acid production of the bacilli coli and paratyphosus.

The determination of the acid death point and the point at which biological activities cease, or are depressed, should be distinguished from the determination of the qualitative fermentative powers of bacteria.

Biometrical studies of fermentation powers of bacteria, in which an arbitrary acid point is spoken of as fermentation while all acid production below this point is neglected, are of great interest as indicating the variable sensitiveness of different bacteria and their ferments to the acids produced, though of little use in determining whether the organism has or has not the power to reduce the carbohydrates. Winslow[9] for streptococci fixed the fermentation point at + 1.2 to phenolphthalein, while Broadhurst uses + 1.5. Streptococci showing acid reactions at or below these points are spoken of as nonfermenters. A reaction of + 0.8 per cent. turns litmus a decided red.[10] What is the source of their + 1.2 or + 1.5 per cent.? I believe it to be the result of the fermentation of the contained carbohydrate. The biometrical system of classification by fermentation tests of Andrewes and Horder[11] and the other English workers is based on qualitative changes. It is true, that subdivisions might be made by the use of further quantitative determinations, but much more must first be learned of the sensitiveness of the bacteria and the conditions of the activity of their enzymes before such a classification is, we believe, advisable. We have found as have many investigators that strains of the bacillus coli recently isolated from water show marked depression in their fermentative powers. Henningsson[12] has shown that cultures of the bacillus coli kept in water for long periods will suffer quantitative loss in their fermentative powers. These depressions are not, however, considered worthy of use in classification.

8. *Centralbl. f. Bakteriol.*, 1911, 59, p. 474.
9. Systematic Relationships of the Coccaceae, New York, 1908.
10. *Ibid.*
11. *Lancet*, 1908, 171, p. 708.
12. *Ztschr. f. Hyg. u. Infektionskrankh.*, 1913, 74, p. 253.

It is well known that different carbohydrates broken up by fermentation give different reduction products. Lactic acid is most constantly found, but oxalic, butyric, acetic, succinic, formic, and other acids are also formed.[13] Moreover, different bacteria break up the same carbohydrate with varying final products.

The fact that bacteria are destroyed by the acids produced in fermentation is well established. It also appears that certain ferments formed by the bacteria are inactive in acid media, or are not formed under the unfavorable acid environment, because the amount of acid produced by the same organism on different carbohydrates varies. Winslow,[14] Fuller and Armstrong,[14] and others, have shown that the amount of acid produced by streptococci from the reduction of dextrose is much greater than that from the more complex carbohydrates, such as lactose, mannite and raffinose. Broadhurst[15] shows that the percentage of acid from salicin is higher than from these three carbohydrates.

The fact that acid is produced by these organisms from the higher carbohydrates, even though the amount is less than from the lower forms, indicates that the power of reducing these carbohydrates is present, and that fermentation does not continue must be due to the presence of the acid products and the lowering of the specific functional activity of the organism or the ferment. Bacterial invertase, for example, is sensitive to acid. Emulsin, however, is not affected by the organic acids (Fuhrmann).[16]

We have used this neutralized acid fuchsin indicator in studying the fermentation of the various carbohydrates; dextrose, maltose, lactose, saccharose, dulcit, raffinose, salicin, mannite, glycerin, dextrin, and others, with a large number of different bacteria including the pneumococcus, streptococcus, the colon-typhoid, and the diphtheria groups, the Gram-negative cocci, and many others, and have found it very satisfactory. The secondary alkali production, among certain of the bacteria, is definitely shown by the decolorization of the indicator. This decolorization is, however, at times, due to the reducing power of the bacteria on the fuchsin. We have noted it particularly among members of the bacillus mucosus capsulatus group. The decoloriza-

13. Gotschlich, Kolle and Wassermann, Handb. d. path. Mikorg., Jena, 1913; Fuhrmann, Bakterienenzyme, Jena, 1907; Lafar, Handb. d. Tech. Mykol., Jena, 1907.
14. Systematic Relationships of the Coccaceae, New York, 1908; *Jour. Infect. Dis.*, 1913, 13, p. 442.
15. *Jour. Infect. Dis.*, 1912, 10, p. 272.
16. Bakterienenzyme, Jena, 1907.

tion, due to the reducing power of the bacteria, appears much less often and at a far later period of growth than when litmus is used.

CONCLUSIONS

The neutralized acid fuchsin indicator as used by Andrade in his glycerin media is applicable for testing the production of acid in the bacterial fermentation of all carbohydrates.

The technic of obtaining a neutral point in media by hot titration with phenolphthalein controlled by the acid fuchsin indicator, showing pink when hot and colorless when cold, gives the most satisfactory results.

Andrade's neutralized acid fuchsin is superior to litmus, as an indicator of acid production in media, on account of its sensitiveness, the sharpness of the change of color (Cohn),[17] and the higher resistance to reduction decolorization. It is particularly useful for teaching purposes.

Titration determinations can be carried out with this indicator at any stage in the growth of the culture.

The use of this indicator in all bacteriological laboratories would give better and more comparable results in studies on the fermentation of the carbohydrates.

Qualitative tests for fermentation are more important than quantitative in the classification of bacteria.

The resistance of bacteria and their ferments to the effects of acid produced in the fermentation process differs with the carbohydrate reduced and with various strains of the same organism. These differences are not, we believe, sufficiently understood to warrant their use in classification.

17. Indicators and Test Papers, New York, 1910, p. 2.

THE RELATIVE LONGEVITY OF DIFFER-
ENT STREPTOCOCCI AND POSSIBLE
ERRORS IN THE ISOLATION AND
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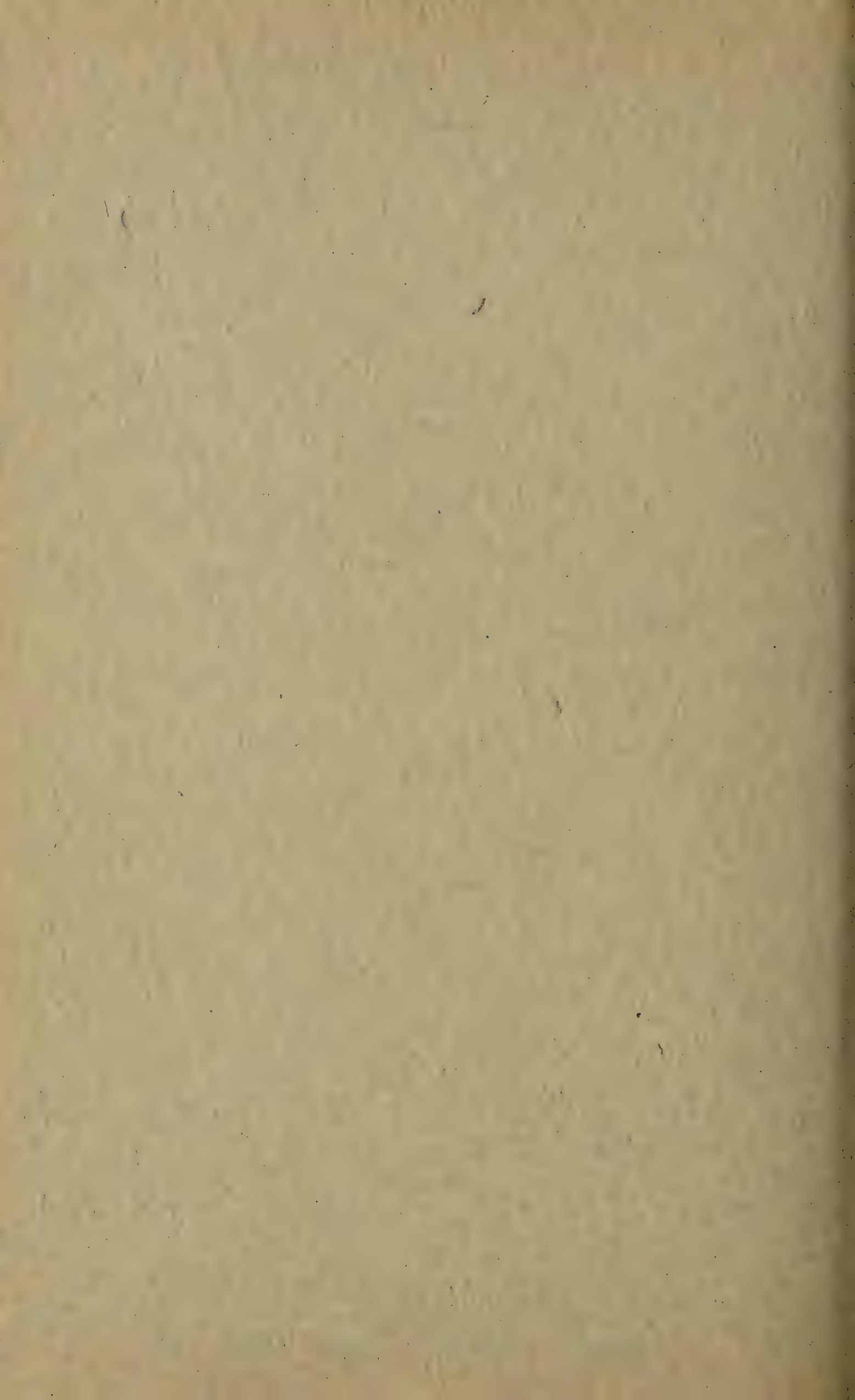
W. L. HOLMAN

THE RELATIVE LONGEVITY OF DIFFERENT STREPTO-COCCI AND POSSIBLE ERRORS IN THE ISOLA-TION AND DIFFERENTIATION OF STREPTOCOCCI *

W. L. HOLMAN

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In the study of a large number of strains of streptococci I am impressed by the marked variation in the viability of the different strains. I have found that many types of streptococci may be stored for months on various media, while on the other hand, one frequently encounters strains that require fresh food material at short intervals.

The most favorable media for the preservation of the life of streptococci are those in which the organisms do not readily produce self-destructive substances. Such media are plain serum broth, blood agar, gelatin and others. It is very important that the media do not contain available carbohydrates as the acids formed by fermentation are detrimental to the life of these organisms.

EFFECTS OF ACID

Numerous investigators have observed the destructive effect of acids on streptococci. Koch and Pokschischewsky[1] used the fact that the streptococcus equi remained living in mannite serum broth after ten days as evidence that it had not attacked the carbohydrate. They also found that, by neutralizing at intervals dextrose and levulose cultures, acid continued to be produced up to the eighth day.

Wurtz and Mosny,[2] believing the rapid death of the pneumococcus in their medium was due to the acid produced, added calcium carbonate, and their cultures remained viable from one to six months.

Hiss[3] used the same method to obtain material for immunization and agglutination. He used dextrose in his medium and added calcium carbonate to prevent the production of an excess of acid.

In another article I have discussed the relative longevity of different streptococci against the acids produced in fermentation. Koch and Pokschischewsky[4] demonstrated that the streptococcus longus was more resistant to acid than the

1. *Ztschr. f. Hyg. u. Infectionskrankh.*, 1913, 74, p. 1.
2. Quoted by Neufeld and Händel, Handb. d. path. Mikroorg., 1912, 4, p. 522.
3. *Jour. Exper. Med.*, 1905, 7, p. 223.
4. *Ztschr. f. Hyg. u. Infectionskrankh.*, 1913, 74, p. 1.

streptococcus equi, as the former remained viable on dextrose broth longer than the latter. Von Lingelsheim[5] has shown that the streptococcus brevis is more resistant than streptococcus longus to hydrochloric, sulphuric and oxalic acids.

EFFECT OF DESICCATION

The effect of drying of the media is important in considering longevity of streptococci. Besides the concentration of the salts and other constituents of the media we have to consider direct action of desiccation. Streptococci vary within wide limits in their power to survive a drying process. The majority of streptococci are very sensitive to desiccation. They usually die in a few days when dried on threads, glass and other substances. Hägler[6] found that streptococci from erysipelas lived from fourteen to thirty-six days when dried on mull, and Kurth,[7] that the streptococcus conglomeratus resisted drying for from five to six weeks. Germano[8] noted that streptococci were very resistant if dried on dust, but different strains showed wide variations in their power to withstand this drying. Andrewes[9] showed that certain strains, such as streptococcus equinus, will live for months when dried on garnets, while streptococcus pyogenes will only live for weeks under the same conditions.

The pneumococcus is generally much more sensitive to drying than the streptococci. Wood[10] has thoroughly studied the viability of the pneumococcus after drying, and many other investigators have shown that its longevity is relatively short.

I have dried a strain of streptococcus fecalis from dextrose broth on cover-glasses and obtained growth after keeping in diffuse daylight for 174 days. The morphologic, cultural and fermentative characters remained unaltered (Holman).[11]

The presence of streptococci in the air is an evidence of their resistance to a relatively high degree of drying. Chatin[12] isolated, from the air of rooms, different kinds of streptococci, some of which were highly pathogenic to rabbits, while others were non-pathogenic. Gordon[13] found several different forms of streptococci in the outdoor air of London, streptococcus brevis being the most common type. Andrewes and Horder[14] have shown that streptococcus equinus is the commonest type present in the air of London. It is also most abundant in horse dung. Rosenow[15] obtained streptococci from the air of the hospital operating-room and the hospital wards. Winslow and Kligler,[16] in a study of

5. Handb. d. path. Mikroorg., 1912, 4, p. 453.
6. Quoted by von Lingelsheim, *Ibid.*
7. *Ibid.*
8. *Ibid.*
9. *Lancet*, 1906, 2, p. 1415.
10. *Jour. Exper. Med.*, 1905, 7, p. 592.
11. *Am. Jour. Pub. Health*, 1913, 3, p. 1210.
12. These-Faculte de Medicine et de Pharmacie de Lyon, 1893, Serie 1, p. 812.
13. *Ann. Rep. Loc. Gov. Bd.*, 1902-3, p. 421.
14. *Lancet*, 1906, 171, p. 708.
15. *Amer. Jour. Obst.*, 1904, 50, p. 762.
16. *Am. Jour. Pub. Health*, 1912, 2, p. 663.

city dust, found in the air a variety of streptococci, chiefly of types character-
istic of the human mouth and the human intestines. These authors conclude
from their studies that certain streptococci are very resistant to drying.

RESISTANCE TO HEAT

Streptococci are also far more resistant to high temperatures than
is commonly supposed. The destructive action of heat on bacteria in
general is, after all, a relative one and we find that streptococci exhibit
a marked variation in their ability to withstand high temperatures.

Van Lingelsheim[17] has demonstrated that the streptococcus brevis is much
more resistant to the action of heat than is the streptococcus longus. The
former withstood 65 C. for twenty minutes, 70 for ten minutes, and 80 for five
minutes, while the streptococcus longus succumbed after twenty minutes at 55 C.,
ten minutes at 60, and five minutes at 67.

In a later article the same author says that if a suspension of streptococcus
longus is heated in normal salt solution to 60 C. for one or two hours it is
not always sufficient to kill all the cocci. One hour at 70 or two hours at 65
is necessary for complete sterilization.

The character and composition of the fluid surrounding the cocci
is of the greatest importance in determining the effects of heat.
Albuminous fluids, such as milk, blood-serum and ascites fluid, have
distinctly protective actions on the contained bacteria. In sterilizing
such fluids for use in the preparation of media, this fact should be
remembered.

In attempts to sterilize beef serum by heating to 56 C. for two hours on four
successive days, I found that certain cocci remained living. On the other hand,
these cocci grown in broth were promptly destroyed within two hours at
56 C. From a batch of milk which had been put through the Arnold steril-
izer for twenty minutes on three successive days, we obtained a streptococcus
mitis which had withstood the high temperature of flowing steam.

In order to further test this protective quality of serum, we used beef serum
diluted one-half with water and sterilized by filtration. To this dilute serum
we added a number of strains of streptococci, allowed the tubes to stand for
ten days at the room temperature, and then heated the tubes to a temperature of
58 C. for twenty-three hours. Only one strain of streptococcus of four used
survived the experiment. This strain had been recently isolated from the feces
of a patient with dysentery and was of the streptococcus fecalis type.

A similar experiment, using ascites fluid and leaving the organisms in con-
tact for only three days, showed that this same strain of streptococcus fecalis
survived heating to 60 C. for six hours. No growths were obtained from any of
the other thirteen streptococci used in this experiment. On a number of
occasions, in attempts to isolate the bacillus Welchii from feces and other mixed
materials by heating to 80 C. for 30 minutes, I have encountered in the cultures,
streptococci, as well as the gas bacillus.

17. Handb. d. path. Mikroorg., 1912, 4, p. 453.

This work will be continued in an endeavor to determine the relationship between the relatively high resistance to heat of certain strains in albuminous fluids to the time of contact, the character of the fluid, the percentage of albumin, the number of organisms added, and other conditions that may have some bearing on the problem.

Ayers and Johnson,[18] in a study of bacteria which survive pasteurization, have made some interesting observations on the resistance of bacteria in milk to high temperatures. These authors have shown that in heating milk to 62.8 C. there was little difference in the bacterial reduction produced by heating for one-half hour and by six hours' heating. The further study of their experiments, in heating samples of milk for a half hour at temperatures of 76.7, 82.2, 87.8, and 93.3 C., shows that their acid-forming group of bacteria, in a high percentage (80.91) survives the temperature of 76.7 C. The percentage is, however, greatly reduced at 82.2 C., and the higher temperatures. In a study of the cultures plated out from milk after pasteurization at 62.8 C. they noted that 89.39 per cent. of the acid-forming group of bacteria were cocci which produced no liquefaction of gelatin. The fermentation reactions of these and further cultures from two series, after heating to 60 C. and 65.6 C. for thirty minutes, would indicate that many of them were streptococci, although the authors do not state the morphologic arrangement of the cocci. This is all the more probable when we consider the frequency and high percentage of streptococci occurring in milk. By the typical lactic acid bacteria as shown in their table of reactions, the authors, no doubt, refer to the so-called streptococcus lacticus.

Frequent attempts have been made to separate the virulent streptococci from the non-virulent forms by the use of various materials, such as lecithin (Fromme,[19] Machtle,[20] and others), but without success. Floyd and Wolbach,[21] following the method of Churchman, have tested out the relative longevity of a series of streptococci in contact with gentian violet and conclude "that susceptibility to gentian violet may be a crude indication of the virulence of the streptococcus." Krumwiede and Pratt[22] show that "the streptococcus-pneumococcus group differ from other gram-positive bacteria in their ability to grow in the presence of amounts of dye sufficient to inhibit the other species," and that the green streptococcus is not as sensitive as the hemolytic strain to the effect of certain dyes.

It is to be recognized that many of the virulent streptococci are more sensitive to a host of influences detrimental to the life of bacteria than are the more saprophytic types or the so-called non-virulent streptococci. This does not, however, hold in all cases and these methods of division of streptococci are being discarded for classification purposes.

LONGEVITY IN SYMBIOSIS

The wide distribution of streptococci and their constant association with other bacteria in the respiratory and intestinal tracts of man and animals in health and disease, as well as their presence in milk and

18. *Bull. Bur. Animal Indust.*, No. 161, 1913.
19. *Zentralbl. f. Gynäk.*, 1909, 33, p. 1217.
20. *Ibid.*, 1911, 35, p. 388.
21. *Jour. Med. Research*, 1914, 29, p. 493.
22. *Jour. Exper. Med.*, 1914, 19, p. 20.

other foodstuffs, make it of peculiar interest to learn something of their longevity in mixed cultures and in mixed infections. I have carried out a number of experiments with mixed cultures of different types of streptococci as well as with mixtures of streptococci and pneumococci and have found that they may live together for long periods of time if frequently transferred. Under unfavorable conditions, such as drying, etc., one or the other type disappears.

STREPTOCOCCI WITH STREPTOCOCCI

In my first experiment I used a strain of streptococcus pyogenes (570) from the pus of meningitis, and a strain of streptococcus fecalis (224) from an old empyema. These cultures were thoroughly mixed on a blood agar slant. Daily transfers were made to fresh blood agar slants and careful notes were kept each day of the appearance of the culture. Blood agar plates were made from time to time, colonies picked, and the freshly isolated cultures were tested for their fermentative reactions. These remained unaltered and distinctive. In this mixed culture hemolysis was the predominant feature up to the fifteenth transfer. On this transfer the blood, in general, was turned green, and with only two areas showing hemolysis. Further transfers showed the gradual return of the general picture of hemolysis, alterations were noted, a few green colonies appearing here and there on the slant at different intervals. On the twenty-ninth transfer there appeared numerous green colonies, but for the next ten transfers only hemolysis was to be seen. In plating on the surface of blood agar plates from these mixed cultures, two methods were used: (1) plates were smeared directly from the blood agar slants; and (2) plates were prepared after a preliminary growth in serum broth.

Several interesting observations were made. Direct plating from blood agar to blood agar usually showed a preponderance of hemolytic colonies and it was difficult at times to find isolated green colonies. Moreover, in picking from plates, showing both green and hemolytic colonies, the transfers from green colonies always proved to be pure, while transfers from the hemolytic colonies were sometimes mixed with the green strain. This is not to be wondered at, when we consider that the two organisms affect the blood in different degrees, one altering the hemoglobin and storing it in its colonies, the other bringing about hemolysis. The streptococcus with its more destructive action on red blood-cells will overshadow the character of the other type when the two are growing together. Moreover, the colonies of streptococcus fecalis are much smaller than those of the streptococcus pyogenes and were often observed within the hemolytic zone and in contact with the pyogenes colonies. The second method of plating, by growing in serum broth before smearing on the plates, allows the cocci to become well separated and the colonies developing are found to be pure. The

number of green colonies developing by this method is also greater, and their presence in the mixture is more easily determined.

STREPTOCOCCI WITH PNEUMOCOCCI

Parallel experiments were made with a strain of pneumococcus (556) obtained from a pneumonic lung at autopsy, and a strain of streptococcus fecalis (369) from feces of a patient with chronic constipation. This strain of streptococcus fecalis produced vegetations on the mitral valve of a rabbit after intravenous injection. The cultures were mixed as in the above experiment and daily transfers of the mixture were made. The pneumococcus colony is larger and more watery than that of the streptococcus fecalis, which is very small and dry. The results show that these two types grow together for long periods and can be reisolated in pure cultures. I encountered the same difficulty as previously noted in isolating colonies on the blood agar plates made directly from the blood agar slants. Transfers from the small green colonies proved to be pure, but those from the larger watery colonies quite frequently showed a mixture. Preliminary growth in serum broth eliminated this difficulty. The growth of the mixture gave the moist appearance of the pneumococcus culture up to the sixteenth transfer and from then until the thirty-ninth showed a more or less regular increase in the dry dotted characteristics of the streptococcus colonies, while here and there a more prominent colony was seen, supposedly of the pneumococcus. The colonies reisolated throughout the experiment were always tested for their fermentative reactions and never showed any alteration from the original strains.

The mixture, after being kept in the incubator for different lengths of time, was tested as a mixture in the carbohydrate serum broth media and usually gave the combined fermentation reactions of both strains. However, from some of the older mixed cultures only the reactions of the streptococcus fecalis were noted.

The pneumococcus remained living up to the last transfer, but it was often impossible to reisolate it from the older cultures. The ability to separate it from the mixture varied apparently with the condition of drying of the medium.

Eight dextrose serum broth tubes were inoculated from the fifth blood agar transfer of the mixture. These were grown for three days at 37 C. Blood agar plates were then made from the dextrose serum broth, but none showed any growth of the pneumococcus. Eight of the largest colonies were picked but they all proved to be the streptococcus fecalis. The high acid production in this medium, due to fermentation, would probably account for the suppression of the pneumococcus.

The growth from these eight tubes was separated by centrifugation, suspended in salt solution, divided equally, and injected into the peritoneal cavity of two guinea-pigs. After forty-eight hours, the guinea-pigs were killed, plates were made from the hearts' blood and 2 to 3 c.c. of blood injected directly into fresh guinea-pigs. The results are shown in Table 1. The pneumococcus was isolated in pure culture. A streptococcus mitis was isolated from the heart's blood of one animal. This result is discussed in a later part of this paper. All the colonies on the blood agar plates from the heart's blood were picked, and the cultures studied for their fermentative reactions. The streptococcus fecalis was not recovered.

The results of these experiments allow us to conclude that the relative longevity of streptococcus fecalis is greater on artificial media

than that of the pneumococcus, and that in the animal body the invasive power of the pneumococcus is greater than that of the streptococcus, or expressed in a different way, the streptococcus predominates on culture media while the pneumococcus gains the ascendancy in the animal body.

SYMBIOSIS WITH OTHER BACTERIA

The symbiotic relationships of the streptococci with other types of bacteria are also of great interest. In the intestinal and upper respiratory tract the streptococci are practically always present, living in closest contact with a host of other bacteria. Cultures from the peritoneal cavity following perforation of the intestines demonstrate that hemolytic streptococci are present in abundance, although cultures from the feces usually show that green-producing streptococci are in the greater numbers. With the bacillus diphtheriae, symbiosis is frequent and important. In obtaining pure cultures of the anaerobes and many other bacteria, streptococci are often difficult to eliminate. There are indeed a few organisms with which one or the other of the streptococci will not live (Gotschlich,[23] Rettger[24]).

Working with a strain of subtilis bacillus, which contaminated mixed culture plates containing pneumococcus and streptococcus, I was able to show that the closest symbiotic relationship can exist for long periods. The colony of bacillus subtilis, which had developed on the more thickly seeded part of the plate, was transferred to a plain agar slant. After 24 hours there was a typical growth of an apparently pure culture of bacillus subtilis. A transfer was made to serum broth and after 24 hours' incubation, a blood agar plate was smeared with the growth. This plate showed the presence of streptococcus, pneumococcus and bacillus subtilis. The small colonies of the cocci were growing close to the subtilis growth, some touching the edge, others apparently within the subtilis colonies, while many were free, scattered in the vicinity. From all three types of colonies, transfers were made and cultures tested out on the various media. The pneumococcus and streptococcus were both recovered in pure culture. From some of the subtilis transfers streptococci were again isolated by plating through serum broth. After ten days in the incubator the mixture on the plain agar was again plated through serum broth and the streptococcus fecalis recovered. The pneumococcus had apparently disappeared. Seven transfers from plain agar to plain agar were made at various intervals and the streptococcus was isolated from each fresh culture of what appeared to be a pure growth of bacillus subtilis. The last plain agar transfer was made forty-one days after the contamination of the blood agar plate. From the second plain agar transfer, after it had been in the incubator for thirty-nine days, a blood agar plate was made through serum broth and the streptococcus was recovered. Colonies were picked from all plates and tested on the carbohydrate and other media. No alteration from the reactions of the original strains was noted.

A hemolytic streptococcus (Streptococcus XII), kindly sent by Dr. Rosenow, was used to test the effect of symbiosis with the bacillus subtilis. Four different strains of the bacillus subtilis group were used. Cross plates were made on blood agar. From the heavy growth of the bacilli, transfers were made to serum broths and from these, after incubation, blood agar plates were prepared. The hemolytic colonies on these plates were unaltered and were to be seen in closest contact with the bacillary colonies. From the serum broths plain agar slants were seeded and apparently pure cultures of the bacilli were demon-

23. Handb. d. path. Mikroorg., 1912, 1, p. 148.
24. *Jour. Infect. Dis.*, 1905, 2, p. 562.

strated. After three days in the incubator, blood agar plates were again made through serum broth. The hemolytic colonies were unchanged on the third, while no growth of the streptococcus could be seen on the fourth. After nineteen days in the incubator on plain agar, blood agar plates from serum broth showed streptococci on only one of the plates. The hemolytic colonies on this plate were, however, typical. No green colonies were seen at any time in this series of experiments. The hemolytic colonies were often in closest contact with those of the bacilli.

From these experiments it would seem that the hemolytic strain of the streptococcus dies out more quickly than the green-producing type.

SECONDARY AND MIXED INFECTIONS

Symbiosis with other bacteria is a well-recognized method of raising the virulence of streptococci and pneumococci (Gotschlich). The study of mixed and secondary infections in human diseases demonstrates that the streptococci and pneumococci play an overwhelming rôle in these conditions. There are certain facts that must be borne in mind. The streptococci and the pneumococci enter the blood under many conditions of lowered resistance. The multiplicity of predisposing causes for pneumonia, the relative ease of streptococcic invasion in rheumatism, the frequency of secondary invasions in scarlet fever (Hektoen,[25] Klimenko,[26] Anthony[27]), typhoid fever (Wassermann and Keyser[28]), tuberculosis (Panichia,[29] Brown, Heise and Petroff[30]), and other conditions of lowered resistance, the invasion in the dead body (Gwyn and Harris,[31] Cannon,[32] White[33]) all bear out this statement. Moreover, it is not uncommon to find the pneumococcus as the cause of secondary conditions in streptococci infections, and vice versa.

SPONTANEOUS STREPTOCOCCUS INFECTIONS IN ANIMALS

What is true of man is also undoubtedly true for laboratory animals. Fatal epidemics caused by streptococci are not at all uncommon. A rapid review of the literature demonstrates this fact.

Charrin[34] found a streptococcus in a rabbit which had died from anthrax. Binaghi[35] isolated a capsulated streptococcus from a guinea-pig which died spontaneously. This was the first reported case of streptococcus mucosus infection. Boxmeyer[36] described a chronic infectious lymphadenitis of guinea-pigs which was caused by a streptococcus. Flexner[37] also found a streptococcus associated with a similar disease in guinea-pigs. Lamar[38] studied sixteen strains of this streptococcus which would indicate that the epidemic was a considerable one. Wittneben[39] studied an epizoötic of guinea-pigs. Twenty-four died and a septicemia with pneumonia, pleuritis and pericarditis was found at autopsy. Streptococcus lanceolatus was isolated from these cases and was differentiated from the human strains of pneumococcus only by its easily stained capsule and its marked coagulation of milk. Weber[40] reports an epidemic of pneumonia

25. *Jour. Amer. Med. Assn.*, 1903, 41, p. 405.
26. *Centralbl. f. Bakteriol.*, Abt. 1, Orig., 1912, 65, p. 45.
27. *Jour. Infect. Dis.*, 1909, 6, p. 332.
28. Handb. d. path. Mikroorg., 1912, 1, p. 645.
29. Baumgarten's *Jahresbericht*, 1908, 24, p. 145.
30. *Trans. Nat. Assn. for Study and Prev. Tuberc.*, 1913, 9, p. 344.
31. *Jour. Infect. Dis.*, 1905, 2, p. 514.
32. Die Bakteriologie des Blutes bei Infectionskrankheiten, Jena, 1905.
33. *Jour. Exper. Med.*, 1899, 4, p. 425.
34. Quoted by LeGros, Monographie des Streptocoques, Paris, 1902.
35. Quoted by Shotmüller, *München. med. Wchnschr.*, 1903, 50, p. 849.
36. *Jour. Infect. Dis.*, 1907, 4, p. 657.
37. Quoted by Lamar, *Jour. Exper. Med.*, 1909, 11, p. 152.
38. *Jour. Exper. Med.*, 1909, 11, p. 152.
39. Baumgarten's *Jahresbericht*, 1907, 23, p. 149.
40. Inaug. Dis., Munich, 1901.

among guinea-pigs. One-half of their rabbits died. At a later period the guinea-pigs became affected and thirty from a stock of fifty died. Streptococci were isolated from all thirty cases. Stephansky[41] described a pneumococcus epidemic among guinea-pigs. The author isolated the pneumococcus from fourteen guinea-pigs, showing at autopsy a purulent and fibrinous inflammation of the lungs.

Selter,[42] in his careful study of natural pneumococcus infection in laboratory animals, reported the isolation of pneumococcus lanceolatus from four guinea-pigs, one inoculated fourteen days before death with a pseudodiphtheria culture, another four days before, with killed tubercle bacilli, and a third after an inoculation two days before with a strain of bacillus dysenteriae. The fourth died spontaneously. Four rabbits also died with coccidiosis and pure cultures of pneumococcus were obtained from the cysts. The following winter another outbreak occurred in which one rabbit succumbed on the fourth day following inoculation with actinomyces, and five guinea-pigs died spontaneously or after the injection of cultures of different organisms. From these six animals pneumococci were also isolated. Lantz[43] speaks of sudden changes of temperature and improper ventilation as common causes of pneumonia in guinea-pigs. It is an extremely fatal disease in these animals. Salomon,[44] in his study of carbohydrate fermentation by the streptococci, includes in his list three strains of pneumococcus from an epidemic in guinea-pigs. Kutschera[45] found a streptococcus in an epidemic among white mice. Weil[46] in his investigations used, among other streptococci, a strain obtained from an epidemic in mice. Wherry[47] reports the finding of streptococci in two white rats. Andrewes and Horder[48] recovered from a mouse, inoculated with a pneumococcus, a gelatin-liquefying strain of streptococcus. These authors emphasize the liability of error in the use of animal passage for experiments on the constancy of the fermentation tests. Lamar[49] studied streptococci from three cases of fatal septicemia in monkeys, and pointed out the great importance of first understanding fully the disease of the laboratory animals.

In my experience, streptococci of various types have been obtained from guinea-pigs injected with other bacteria, and from guinea-pigs which died spontaneously. In Tables 1 and 2 the results of my experiments are given in condensed form. From these examples, as well as from the number of reports cited from the literature, it can reasonably be inferred that an invasion of the animal body by the streptococcus-pneumococcus group occurs under natural conditions, as well as from the injection of cultures of various bacteria. The strain of streptococcus mitis recovered from the heart's blood of Guinea-pig 6 was not, I believe, either a transformed pneumococcus or an altered streptococcus fecalis any more than the streptococci from the heart's blood of Guinea-pig 8, and those from the peritoneal cavity of Guinea-pigs 9 and 13 were derived from the dead or living cultures of the

41. Quoted by Selter, *Ztschr. f. Hyg. u. Infectionskrankh.*, 1906, 54, p. 347.
42. *Ibid.*
43. *Farmers' Bull. from U. S. Dept. Agricul.*, No. 525.
44. Inaug. Dis., Kiel, 1901, 8.
45. Baumgarten's *Jahresbericht*, 1908, 24, p. 136.
46. *Ztschr. f. Hyg. u. Infectionskrankh.*, 1911, 68, p. 346.
47. *Jour. Infect. Dis.*, 1908, 5, p. 515.
48. *Lancet*, 1906, 171, p. 708.
49. *Jour. Exper. Med.*, 1909, 11, p. 152.

TABLE 1

STREPTOCOCCI RECOVERED FROM INOCULATED GUINEA-PIGS

No.	Intraperitoneal Injection of	Result	Characteristics of Isolated Streptococci					
			Chains	Hemolysis	Lactose Serum Broth	Mannite Serum Broth	Salicin Serum Broth	Inulin Serum Broth
1	5 c.c. serum broth cultures of streptococcus from vagina†	Death after four days; streptococci isolated from peritoneum	Long	Green	+	+	+	+
2	5 c.c. serum broth culture from Guinea-pig 1	Death after 3 days; streptococci from peritoneum	Long	Green	+	+	+	+
3	Mixed culture of pneumococcus and streptococcus fecalis	Killed after 48 hours; cultures sterile	....	....	:	:	:	:
4	Same as No. 3	Killed after 48 hours; pneumococci from blood	—	Green	+	—	+	+
5	3 c.c. of blood from No. 4	Killed after 48 hours; pneumococci from blood	—	Green	+	—	+	+
6	3 c.c. of blood from No. 5	Killed after 48 hours; streptococci from blood	Medium	—	+	—	+	—
7	2 c.c. of blood from No. 5.	Killed after 48 hours; pneumococci from blood	—	Green	+	—	+	+
8	2 agar slants of colon bacilli	Died in 15 hours; colon bacilli and streptococci from blood	Short	—	—	—	+	—
			Long	—	—	—	+	+
			Short	—	+	—	+	—
9	3 agar slants of colon bacilli heated 60 degrees for 1 hour	Killed in 48 hours; streptococci from peritoneum	Medium	—	+	+	+	—
10	20 c.c. dextrose serum broth culture of streptococcus 659	Killed in 48 hours; cultures sterile	....	....	:	:	:	:
11	50 c.c. dextrose serum broth culture of streptococcus from guinea-pig intestine‡	Killed in 48 hours; blood peritoneum; streptococci	Medium*	—	+	+	+	—
			Short**	—	—	+	+	—
12	Agar slant of colon bacillus	Killed in 16 hours; no growth	....	....	:	:	:	:
13	Peritoneal fluid from No. 12	Dead in 6½ hours; streptococci from peritoneum	Long	—	+	+	+	—

* From blood.   ** From both blood and peritoneum.

† Hemolysis positive; lactose and salicin positive; mannite and inulin negative.

‡ Hemolysis negative; mannite and salicin positive; lactose and inulin negative.

TABLE 2

STREPTOCOCCI FROM GUINEA-PIGS DYING SPONTANEOUSLY*

No.	Anatomical Changes	Cultures	Characteristics of Isolated Streptococci					
			Chains	Hemolysis	Lactose Serum Broth	Mannite Serum Broth	Salicin Serum Broth	Inulin Serum Broth
1	Normal	Streptococci from cervical gland	Medium	+	—	—	+	—
2	Normal	No streptococci	—	—	—	—	—	—
3	Normal	Sterile		:	:	:	:	:
4	Pneumonia, pleuritis, congestion of small intestine	Streptococci (Peritoneum, Pleura, Blood)	Short†	—	+	+	+	—
5	Pneumonia	Streptococci from pleura and blood	Long‡	+	+	—	+	—
6	Pneumonia	Streptococci from pleura and blood	Long	+	+	—	+	—
7	Pneumonia, pleuritis	Streptococci from pleura and blood	Long	+	+	—	+	—
8	Pregnancy	Pseudodiphtheria bacilli from blood	..	:	:	:	:	:

* These guinea-pigs were those dying spontaneously from a stock of about 700.
† From peritoneum.
‡ From pleura and blood.

TABLE 3

CHARACTERISTICS OF STREPTOCOCCI OBTAINED FROM GUINEA-PIGS

Source	Chains	Hemolysis	Lactose Serum Broth	Mannite Serum Broth	Salicin Serum Broth	Inulin Serum Broth	Notes
Intestinal Contents	Medium	—	—	+	+	—	
Intestinal Contents	Medium	—	+	+	+	+	See Nos. 1 and 2, Table 1.
Intestinal Contents	Medium	—	+	+	+	—	See Nos. 9, 11, 13, Table 1, and No. 4, Table 2.
Throat	Short	—	—	—	+	+	
Throat	Short	—	+	+	+	—	
Throat	Long	—	+	+	+	+	See No. 8, Table 1.

bacillus coli. In 1910, I recovered from the peritoneal cavity of a guinea-pig injected with a hemolytic streptococcus from the vagina, a non-hemolytic streptococcus which fermented inulin. I concluded that this organism had come from the animal.

Members of the streptococcus-pneumococcus group are found regularly in the intestinal and upper respiratory tracts of most animals (Selter,[50] De Gasperi,[51] and others). I have isolated members of this group from the intestines and upper respiratory tract of a number of normal guinea-pigs. The cultural characteristics of these streptococci are shown in Table 3.

Many investigators have demonstrated by experiments the comparative ease with which organisms pass from the intestinal canal of animals into the blood-stream and the organs of the body. Loiseleur,[52] Sacquepee and Loiseleur,[53] Basset and Carre,[54] Garnier and Simon[55] and others have shown that various methods of lowering the resistance by heat, cold, inanition, overexertion, injections of toxins, hypertonic solutions, dilute acids, and other conditions, lead to a bacteremia.

Adami[56] has shown that the tissues are potentially, but not actually, sterile. In animals fed with various cultures of bacteria these can be obtained, after a few hours, from the various organs of the body, for during the digestive process bacteria are absorbed along with the food, especially when much fat is present. Acute congestion of the mucosa of the intestines, however brought about, favors the passage of bacteria.

Simmonds[57] found that, after injecting rabbits with 500,000 to 2,500,000 killed streptococci, he had first a fall, then a rise in the opsonic index, and it is well known that injections of large numbers of bacteria regularly bring about a fall in the opsonic index. Young animals have been shown to be more susceptible to invasion than the full grown.

MUTATIONS

Buerger and Ryttenberg[58] believed that they had observed newly acquired properties in many of their strains of pneumococcus. It is interesting to note that in their first case the blood culture tested was taken two days before death and that this culture was readily converted from an atypical into a typical pneumococcus by passage through mice. A strain isolated from a metastatic abscess of this case showed the same general cultural characters. This latter strain could not be converted, and the former, after the lapse of one month, was also non-convertible. The authors state that the colonies from this blood culture showed "some ring forms" and that the morphology was "like degenerated pneumococci." I would conclude that the writers were dealing with a mixed infection in the blood culture, and a pure infection in the metastatic abscess. This explanation, based on the results of my experiments, as recorded in the earlier part of this paper, as well as on experience with mixed infections with pneumococcus, will serve to clear up the apparent confusion of the other cases cited by these authors.

Rosenow[59] in a recent communication claims that he has been able to transmute the pneumococcus to streptococci of various types, and vice versa.

50. *Ztschr. f. Hyg. u. Infectionskrankh.*, 1906, 54, p. 347.
51. *Centralbl. f. Bakteriol.*, I, Orig., 1911, 57, p. 519.
52. Baumgarten's *Jahresbericht*, 1906, 22, p. 812.
53. *Ibid.*, 1907, 23, p. 703.
54. *Ibid.*, 1908, 24, p. 962.
55. *Ibid.*, 1909, 25, p. 969.
56. *Jour. Amer. Med. Assn.*, 1899, 32, p. 1509; *Br. Med. Jour.*, 1914, 1, p. 177.
57. *Jour. Infect. Dis.*, 1907, 4, p. 595.
58. *Ibid.*, p. 609.
59. Ibid., 1914, 14, p. 1.

Schereschewsky[60] believes that the streptococcus pyogenes is closely related to the pneumococcus. He was able to bring about very marked morphologic changes and believed he was able to change one form into the other. Schereschewsky's results have not been accepted as indicating any fundamental alteration of these organisms.

Rosenow has gone much further and he is convinced that "the transformations of some of the strains are complete by every known test." He has not only altered the morphology, the formation of capsules, and the fermentative powers, but also the specific immunity response, and the more or less specific pathogenic powers. The results of my experience and those of numerous other workers would tend to throw doubt on many of his interpretations.

In the detailed description of some of his experiments I am able to follow some of the steps of his transmutations. In Strain 595 he had a hemolyzing culture which, after growing for over a year and showing no important change during this time, was transferred to blood agar slants and left in the incubator twenty-nine days until "the media were very dry." Transfers were now made to fresh blood agar, and after eight days at 37 C. the surface of a smeared blood agar plate showed two types of colonies, one hemolyzing, and the other not. This would appear to the ordinary observer to have been either from a survival of a non-hemolyzing strain, as shown in my experiments, or to have been a contamination. These non-hemolyzing colonies were first noted on November 15. On November 17, four colonies of each variety were plated on blood agar plates. One of the non-hemolyzing colonies, thus plated, showed on November 19 two types of colonies, adherent and non-adherent. On this same date, before these two types of colonies had been studied further, Rosenow injected four small rabbits (600-750 gm.) with the growth from 20 to 60 c.c. of ascites dextrose broth culture of this streptococcus viridans strain. One colony from the blood of one of these rabbits was used for the further transmutation into pneumococcus. On November 21, transfers were made from the culture of an adherent green colony to blood agar and Loeffler's serum. After seventy-seven days the growth on Loeffler's serum yielded both hemolyzing and non-hemolyzing colonies. Is this evidence of reversion or the indication of a mixed culture? The author does not give the fermentative and other characteristics of these various strains when first isolated as a streptococcus viridans, when recovered from the first injected rabbit, nor after the first two guinea-pig injections. The transformed pneumococcus, after being subcultured for five months, yielded a hemolytic strain which showed fermentation of mannite, a reaction not shown by either the original hemolytic strain or the pneumococcus. In such an important question as the conversion of such well differentiated organisms as the pneumococcus and the hemolytic streptococci, full and complete cultural and other characters should be given at every step in the alteration. That the organisms at the beginning and at the end of the experiment are quite different in every important character we have no doubt, but if transmutation has really occurred, we must know when the changes took place.

The transmutations by growth with the bacillus subtilis we have been unable to confirm, although we used a hemolytic strain (XII) kindly sent me by Dr. Rosenow, and cultured it in intimate contact with four strains of the subtilis bacillus. We were, however, able to show that a strain of streptococcus fecalis grew with the bacillus subtilis for long periods of time, and could be best recovered by plating on blood agar after first growing the mixture in serum broth. Strain XII as a hemolyzer, had been converted by Rosenow into strep-

60. *Centralbl. f. Bakteriol.*, Abt. 1, Orig., 1909, 49, p. 72.

tococcus viridans by growth in symbiosis with the bacillus subtilis. The full characteristics of the three varieties of colonies, obtained from this strain after growth on ascites-dextrose agar, are not given. It is to be noted that ascites fluid seemed to be necessary for the alteration into the rheumatic types of strepto-cocci with this and other strains discussed under "the effect of growth in a high oxygen pressure." The author used in his media, in the study of the etiology of acute rheumatism, ascites fluid which yielded uniform and frequent positive results. The very uniformity is striking. In one case he obtained two colonies per 20 c.c. from the right knee, two colonies per 12 c.c. from the left knee, three colonies per 2 c.c. from the wrist, and ten colonies per 0.05 c.c. of bloody fluid from a red, tender, swollen area over the lower end of the ulna. Is it possible that the ascites fluid was not sterile? The method of heating to 60 C. for twenty-four hours to obtain sterile fluid is not as certain as careful filtra-tion. In testing such a fluid for the presence of a few organisms, large quanti-ties must be employed. Recently I obtained from a peritoneal swab, taken at operation, a strain of streptococcus which showed a marked tendency to anae-robism. It grew best in the depths of carbohydrate serum agar media and did not develop on the surface till after several transfers. It did grow, however, in very minute colonies on fresh blood agar slants. Unfortunately, the resist-ance to heat of this streptococcus was not tested. Such an organism would be readily overlooked in testing the sterility of human fluid for use in culture media.

Strain 734 was claimed to have been changed by aerobic culture in distilled water from a non-mannite green-producer into a hemolyzer and mannite fer-menter. Its virulence was also distinctly greater than before. The raising of virulence by growth in water is contrary to the experience of all workers in water bacteriology.

From my experiments with guinea-pigs, and the results of the other investi-gators cited, I would be unwilling to believe that the recovery of green strep-tococci from a joint, or the pericardium, or other cavities of animals injected with large doses of a hemolytic streptococcus, is sufficient evidence to conclude that the recovered organism is the same as that injected.

The altered form of Strain 734, which was subsequently changed to pneu-mococcus, was derived from the pericardium of a rabbit. Strain 736 "in the joint of one rabbit, in its second passage, lost the power to hemolyze and produced green colonies instead." When Strain B, a "pure line," which had acquired the power to hemolyze blood agar, was recovered from the joint of one rabbit it was found mixed with green streptococci. This latter strain was then trans-formed into pneumococcus. Strain R 51A was originally a pneumococcus, but had acquired the power on dried blood agar to hemolyze blood for the first time in over ten years. This strain was passed through sixteen rabbits. The joint culture from the sixteenth animal showed both green and hemolyzing colonies. A hemolytic streptococcus, derived from a pneumococcus, was injected into a rabbit, which five days later was found dead. Joint fluids yielded three green and no hemolyzing colonies.

The number of guinea-pigs used, before the transmutation of strains of strep-tococcus viridans into pneumococcus took place, varied greatly. My interpreta-tion of this fact is that the invasion from the animal varied with the different animals, or the invading organisms were not recovered until they had gained a numerical ascendancy.

Andrewes,[61] in an excellent paper, has discussed the nature and degree of specific differences amongst bacteria, and his points are well

61. *Lancet,* 1906, 2, p. 1415.

worth consideration for maintaining a conservative view of the questions of differentiation of bacteria.

CONCLUSIONS

Streptococci vary within wide limits in their longevity on artificial media. They also show wide differences in their sensitiveness to the effects of desiccation.

The presence of acid, produced in media containing carbohydrates, is very detrimental to the life of streptococci. The widest variation is exhibited among different strains to this effect of acid.

Many strains of streptococci are resistant to high temperatures over prolonged periods of time, more especially when protected by albuminous fluid as in milk, beef serum and ascites fluid.

Streptococci of all forms live in closest symbiotic relationship with many other bacteria.

Hemolytic streptococci, growing on blood agar in mixed culture with a green-producing form, show an apparent predominance, and pneumococcus and streptococcus, in mixed cultures, show that the growth of the pneumococcus may be overshadowed by that of the streptococcus.

Plating on blood-agar after a preliminary growth in serum broth is a more certain method for obtaining pure cultures than direct plating from blood-agar to blood-agar.

The injection of known mixed cultures of pneumococcus and streptococcus, which culturally appear to be pure streptococcus, shows that the more invasive form, the pneumococcus, survives.

In mixed cultures of pneumococcus and streptococcus fecalis the former disappears first, as the result of drying of the media.

Strains of green streptococci will live for long periods in mixed cultures with the bacillus subtilis, while the pneumococcus and hemolytic streptococci die out more quickly.

The growing of hemolytic streptococci with cultures of the bacillus subtilis for long periods has no effect in altering its hemolytic properties.

Streptococci and pneumococci invade the body under many and various predisposing conditions. They are also by far the most frequent secondary invaders.

These organisms spontaneously invade the bodies of our laboratory animals bringing about fatal epidemics. Various predisposing causes make these invasions possible.

The intestinal and upper respiratory tracts of guinea-pigs contain different forms of streptococci.

Injections of bacteria into guinea-pigs, especially young animals, bring about an invasion into the body cavities and the blood-stream of organisms, more particularly of various strains of streptococci derived from the normally infected regions of the animal.

Isolation from animals of streptococci, differing in important characteristics from those injected, cannot be taken as proof of a change in the characteristics of the injected streptococcus within the animal body, owing to the ease with which streptococci are able to enter the tissues from the intestines or respiratory tract of animals as well as man.

In attempts at transmutation all the characteristics of the organisms must be given at every stage of the experiment.

A METHOD FOR MAKING CARBOHY-
DRATE SERUM BROTH OF CON-
STANT COMPOSITION FOR
USE IN THE STUDY OF
STREPTOCOCCI

W. L. HOLMAN

A METHOD FOR MAKING CARBOHYDRATE SERUM BROTH OF CONSTANT COMPOSITION FOR USE IN THE STUDY OF STREPTOCOCCI

W. L. Holman

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For several years I have been studying the cultural and biological characters of the streptococcus group of the coccaceae, and have given particular attention to the development of the most favorable medium.

I learned very early in the work that in order to obtain good growth of the streptococci, fluid media were preferable to solid media. I also soon learned that the addition of serum to the media enhanced very markedly the development of the streptococci. It was often observed that exudate from appendiceal and other peritonitis cases showed in direct smears a mixture of Gram-negative bacilli and Gram-positive streptococci. Part of this material was added to plain broth and part to serum broth, and on examination of the growth in twenty-four hours or less the microscopical pictures from the two media were very different. That from the plain broth showed a predominance of Gram-negative bacilli with very few Gram-positive cocci, while the smear from serum broth showed what often appeared to be a pure culture of streptococci. From feces, one obtains practically the same results, that is, in the serum broth, the streptococci developing are numerous, while in plain broth they are almost absent.

That the addition of serum increases the growth of streptococci is, of course, well known. Elschnig[1] employed it in making cultures from the conjunctiva, and the high percentage (30) of streptococci which he obtained from apparently normal eyes is undoubtedly due to the use of the serum medium.

In studies on the pneumococcus the use of serum media was early recognized as necessary and was widely employed.

Hiss[2] used serum in his serum water media which were made as follows: Beef serum one part, distilled water two or three parts, heated in the Arnold sterilizer for 12 minutes at 100 C. One per cent. of a 5 per cent. aqueous solution of litmus was added until a deep transparent blue was obtained. One per cent. of the sugar to be used in the test was added to this medium. The serum water media were sterilized by the fractional method of 100 C.

1. *Deutsch. med. Wchnschr.*, 1910, 26, p. 1229.
2. Hiss and Zinsser, Text-Book of Bacteriology.

Buerger,[3] modifying these media by adding about 2 per cent. peptone, obtained better results in growing the pneumococcus than with Hiss' serum waters.

Ruediger[4] further modified the serum water media. He employed beef serum which was diluted with an equal volume of water, passed through a large Berkefeld filter, heated to 65 C. for one-half hour on two successive days, and added in equal amounts to the previously tubed and sterilized litmus carbohydrate peptone and salt solution.

Buerger,[5] in an article on the differentiation of streptococci, points out that the addition of ascitic fluid not only enhances growth but seems to favor the fermentation of certain of the carbohydrates that were not attacked in the simple media (sugar free broth), and lays emphasis on the use of the most favorable media for the growth of these organisms in doing the fermentation tests.

Heinemann[6] used serum broth for "rejuvenating" the streptococcus lacticus before injecting it into rabbits. Marmorek used various strengths of different sera for producing rich and virulent cultures of streptococci, recommending equal parts of peptone broth and human serum as the best.

In an attempt to differentiate the large numbers of streptococci that were obtained in this laboratory carbohydrates were used as recommended by Gordon.[7] The media used differed, however, in that the broth was made from Liebig's meat extract and serum added in the proportion of one part serum to four of the broth. The serum employed was usually hydrocele fluid but ascitic and ovarian fluids were also used. The two latter were very often found to be of little use in enriching our media. All three sera were moreover quite inconstant in their albuminous content and the results obtained were, at times, quite irregular. This led to the attempt to make a serum broth on which one could rely for always obtaining a good growth of streptococci. After we had tried several of the serum waters and found them, although a decided improvement on plain broth, not as satisfactory as the serum broth, the following serum medium was prepared which was later improved.

Beef blood was collected from the abattoir in sterile quart jars, such as are commonly used for storing preserves, called lightning jars. The blood was allowed to clot in the cool room of the abattoir for about 15 minutes. It was then brought to the laboratory, rimmed, and allowed to stand overnight in a cool place. The clear serum was obtained by centrifugalization, after which it was ready for use. One hundred c.c. of this serum was added to 300 c.c. of distilled water, and sterilized for 15 to 20 minutes in flowing steam on three successive days. The mixture became slightly milky or opalescent but was perfectly transparent.

3. *Jour. Exper. Med.*, 1905, 7, p. 524.   5. *Jour. Exper. Med.*, 1907, 9, p. 428.
4. *Jour. Infect. Dis.*, 1906, 3, p. 756.   6. *Jour. Infect. Dis.*, 1907, 9, p. 87.
7. *Ann. Rept. Loc. Gov. Bd., London*, 1903-4, p. 388.

The carbohydrate broth was made as follows:

Peptone (Witte)	40	gm.
Meat extract (Liebig's)	12	"
Sodium chlorid	20	"
Distilled water 1,000		c.c.

This broth was four times the usual strength. It was made neutral to phenolphthalein (hot titration) and 4 gm. of the carbohydrate and 4 c.c. of Andrade's indicator were added to 100 c.c. This broth was sterilized in flowing stream for 15 to 20 minutes on three successive days.

The sterile serum water was then mixed with this quadruple strength carbohydrate broth, and the medium, consisting of 1 part serum to 4 parts 1 per cent. carbohydrate broth, was tubed into sterile tubes by means of a sterile tubing-funnel, or by use of a sterile syphon. The use of the syphon was as follows: The 500 c.c. of carbohydrate serum broth was mixed in a large flask. A rubber cork was fitted with a syphon and a glass tube bent at right angles, the outer end of which was plugged with cotton wool. This apparatus was sterilized in another flask, transferred to the flask containing the medium, the syphon started by blowing through the bent tube, and the medium tubed into sterile tubes.

This medium gives a much better growth of streptococci than the serum waters or ordinary broth. It is coagulated on the production of acid in the fermentation of the carbohydrates as is the case in all heated serum media (Longcope).

The heating of the serum undoubtedly alters many of its albuminous constituents, possibly they are changed into the so-called colloidal state as Longcope[8] suggests. Whatever the change, it is not as favorable a medium for streptococcus growth as the unheated serum.

In order, therefore, to obtain a medium containing unheated serum it was decided to sterilize the serum by filtration. It was found, however, that the filter became clogged after a relatively small amount of the serum had passed through. To overcome this, the serum was diluted one-half with distilled water and it now passed without any difficulty through an ordinary Berkefeld filter. To assure sterility, it is important that the filtration takes place slowly as otherwise organisms pass through the filter candle.

A very useful addition to the ordinary filtering apparatus is the insertion of a large glass tube into the rubber cork of the filtering flask to direct the filtered serum past its side opening. Also a large inverted test tube covering the filter candle makes possible the filtration of the last of the serum without the bubbles that are commonly formed.

The carbohydrate broth with which the serum was subsequently mixed was made up as follows:

Double strength broth + 1.2 ac......................	200	c.c.
Distilled water	100	c.c.
Carbohydrate	4	gm.
Andrade's Indicator	4	c.c.

Sterilized in flowing steam 15 to 20 minutes on three successive days, cooled and then 200 c.c. of the diluted and filtered serum added.

The finished medium gave a carbohydrate serum broth. It was tubed as above described and was incubated for several days before use to ensure sterility.

8. *Jour. Exper. Med.,* 1905, 7, p. 131.

Different strengths of serum are easily obtained by varying the above formulae. The dilute serum obtained as described above is very useful to add to carbohydrate agar for anaerobic cultures.

The advantages of this method for making serum broth are: (1) A uniform mixture is obtained in all tubes; (2) there is less liability for contamination than by the use of sterile pipets and the addition of the serum to each tube; (3) the serum used has never been heated and is, therefore, unaltered; (4) the use of beef serum assures a serum of reasonably constant composition and it is, therefore, useful for comparative tests. Moreover, as Longcope[9] has pointed out, beef serum does not show the production of acid with the growth of pneumococcus and in my experience acid is never produced in the control sugar-free serum broth with a great variety of streptococci; (5) this serum medium is not coagulated by the production of acid, only a slight opalescence appearing when much acid is produced.

I have carried out a number of experiments with the streptococcus by growing it in ordinary carbohydrate broth and in the carbohydrate serum broth, and our results have been striking. I have found that many strains of streptococci fail to grow at all while others grow very poorly in ordinary broth. It is true, on the other hand, that a great number grow well in both media, but always more luxuriantly in the serum broth. It is, I believe, fundamental in the study of the fermentation reactions of the streptococci, to have a medium in which the organisms grow well independently of the carbohydrate added. Although many of the streptococci will ferment a certain carbohydrate in broth, serum water, or serum broth, others grow so poorly in the former that they fail to attack the carbohydrate, and the result would appear negative if no further study were undertaken.

In a recent article Broadhurst[10] has shown that she gets a higher acidity in meat than in meat extract broth. It is well known that meat infusion broth makes a better medium for sensitive organisms than meat extract broth, and I would be inclined to believe that she was dealing with a more vigorous growth in the former case.

Floyd and Wolbach[11] on the differentiation of streptococci say, "We are not certain that the clotting of milk is solely dependent upon carbohydrate fermentation. This is tentatively offered in the light of our experience in that milk may be acidified without acid production in dextrose and lactose serum waters." It is interesting to note in this connection that out of 63 strains in their Group 2, 29

9. Ibid.
10. *Jour. Infect. Dis.*, 1913, 13, p. 404.
11. *Jour. Med. Research*, 1914, 29, p. 493.

show acid in milk and 34 clotting of milk without producing any acid in lactose. In Group 4, they found that out of 42, 8 produced acid and 3 clot in milk, without acid in lactose serum water. In Group 5, out of 43, only 1 produced clot in the milk without acid in the lactose medium. In Group 6, the results in milk and in lactose serum water are the same with the exception that two strains failed to affect either the milk or the lactose serum water.

Group 2 "corresponds closely to streptococcus pyogenes." Group 4 is composed of non-hemolytic strains and is "intermediate between streptococus pyogenes and the streptococcus anginosus." Group 5 "corresponds closely to streptococcus anginosus."

The more strictly parasitic streptococci are grown with greater difficulty in artificial media and I would suggest for these confusing results the explanation that the growth in the lactose serum water is not vigorous enough to allow the organisms to exert their fermentative powers, while in the milk the conditions for growth are more favorable and the organisms ferment the contained lactose and dextrose. The explanation of the results of Group 1, where no fermentative action was demonstrated or only acid was developed in dextrose, is more difficult as milk is not affected. "These cultures come mostly from cases where the streptococcus played a pathogenic role." I have met in investigations of about 500 strains a fair number (25) of streptococci which failed to ferment lactose, but which hemolysed blood. They are similar to the 44 out of 62 strains observed by Floyd and Wolbach. I have also encountered a few strains (12) which do not hemolyse and which correspond to the streptococcus equinus of Andrewes and Horder.[12] However, I have always noted a slight acidity in litmus milk and acid was formed in the dextrose and saccharose serum broth. The five strains in Group 3 and one in Group 5, as reported by Floyd and Wolbach,[13] which appear to ferment the lactose in the serum water media but fail to affect any change in milk, are interesting and would bear further investigation.

Winslow and Palmer,[14] in a comparative study of intestinal streptococci, "utterly failed" to isolate streptococci from feces by growing in dextrose broth preliminary to plating on agar and resorted to plating on agar directly, which method "proved generally successful."

From my experience, I feel certain that the use of serum broth would have materially helped them in their isolations. These workers also had in their carbohydrate broth fermentation tests a considerable number of "clear tubes" in which no obvious growth of the streptococci had occurred. These tubes were plated out on agar with the result that out of 49 tubes plated "3 showed many colonies, 15 showed 1 to 6 colonies, and 31 showed none." "It may reasonably be assumed," they say, "that in such cases the streptococci introduced had simply failed to develop and gradually died out on account of the lack of suitable carbohydrate pabulum, on which these organisms appear to be highly dependent." It would seem that these streptococci which failed to develop and others in which feeble growths had occurred had not been given the most favorable environment in which they could demonstrate their fermentative powers.

Salomon[15] and other German workers in studying the fermentative powers of the streptococci have used litmus ascites carbohydrate agar. Their results are very different from those obtained by others where fluid media were employed. Salomon found that 13 strains of the pneumococcus and 6 out of 10 of his strains

12. *Lancet,* 1906, 2, p. 708.
13. *Jour. Med. Research,* 1914, 29, p. 493.
14. Systematic Relationships of the Coccaceae.
15. *Centralbl. f. Bakteriol.,* Abt. I, Orig., 1908, 47, p. 1.

of streptococcus mucosus practically failed to show any fermentative powers by his method, although he used 18 different carbohydrates. These organisms are well known to have high powers of fermentation, and the results Salomon obtained are due, we believe, to the use of solid in preference to fluid media.

Winslow[16] in his study of the coccaceae draws attention to the fact that in obtaining material by the method of plating on agar and incubating at 20 C. he failed to obtain many of the more strictly parasitic streptococci which grow only feebly on solid media and are most active at a temperature of 37 C. In this I agree perfectly, but would go further and say that I believe a study of streptococci without the use of serum broth loses much of its value, from failure to isolate many of the less easily grown strains, and furthermore, many are not given a sufficiently rich medium in which they may develop vigorously enough to exercise their fermentative action on the contained carbohydrate.

There is a well recognized difference in cells in respect to their ability to exercise their specific functions. These functions may be ⸱irely absent where the cells are merely living or even slowly repro- ꞌꞌcing. A healthy state of the cell where both reproducing and functional activities are at their highest is to be found only where the environment is best suited to the needs of the cell.

This is well known when we consider the functional activity of the cells in the metazoa and is, I believe, equally true among the unicellular organisms now under discussion.

CONCLUSIONS

Serum broth is the most favorable medium for the isolation and growth of streptococci. It is so well suited to the growth of streptococci that in mixed cultures, even vigorous organisms such as the bacillus coli are overgrown in twenty-four hours.

Cultures containing different forms of streptococci should be planted in serum broth for at least twenty-four hours before plating on blood agar. If this is not done, many of the more pathogenic forms are liable to be overlooked.

Many strains of streptococci grow poorly in plain carbohydrate broth while others fail to show any growth at all.

In testing the fermentative powers of streptococci the carbohydrates should be added to serum broth.

The method here described offers a means for making a carbohydrate serum broth of reasonably constant composition, and which, in my hands, has always given a good growth of streptococci.

16. Systematic Relationships of the Coccaceae.

EXTENSIVE PIGMENTATION OF THE BRAIN ASSOCIATED WITH NEVI PIGMENTOSI OF THE SKIN

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EXTENSIVE PIGMENTATION OF THE BRAIN ASSOCIATED WITH NEVI PIGMENTOSI OF THE SKIN.[*]

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Rokitansky, in 1861, reported a very unusual and interesting case of a pigmented nevus of the skin associated with marked pigmentation of the brain. The condition occurred in a young girl fourteen years of age. The skin lesion was a typical pigmented nevus both macroscopically and microscopically. In the brain a diffuse brownish-black pigmentation of the arachnoid and pia mater and of the ependyma of the ventricles was present. Here and there small nodules of pigment the size of millet seeds were scattered over these areas. Pigment was not present in any of the other organs. Microscopical examination from the involved brain showed that the pigment lay in spindle and branched cells in the form of round granules. Rokitansky further noted a marked perivascular arrangement of the pigment cells.

A somewhat similar case has been reported by Oberndorfer. Here, however, the pigmentation both in the skin and brain was decidedly more intense. Oberndorfer's case was in a child of eight months. There were numerous deeply pigmented nevi scattered over the skin; microscopically the nevi were not remarkable. In the brain, pigment spots were seen in the cerebrum, optic thalamus, floor of the fourth ventricle, while there was also a very diffuse and extensive pigmentation of the cerebellum. Microscopically the brain showed, in the involved areas, numerous round and large cells containing much granular pigment. Oberndorfer considered his case as illustrating primary nevus formation of the skin and brain, and in no sense was the pigmentation of the central nervous system to be regarded as a metastasis from the skin. The origin of the nevus cells in both situations

was considered as epithelial, on one hand from neuro-epithe-
lium and on the other from the epidermis.

The third and last case that we have been able to find in
the literature is one reported by Grahl. As this is almost
identical with ours we shall describe it in more detail. It
occurred in a new born child. There was a very large pig-
mented nevus in the skin over the lower part of the abdo-
men and thighs. Smaller nevi were scattered elsewhere
over the surface of the body and the extremities. Micro-
scopically the skin nevi showed nothing of particular note,
although the author lays stress on the close proximity of
the nevus cells to the deep layers of the epithelium. The
stroma of the nevus he looked upon as a development of
the connective tissue of the part and not derived from the
nevus cells. In the brain the pigment lay in the form of
brownish spots in the inner side of the optic thalamus, in the
corpora quadragemina, and on the floor of the fourth ventri-
cle. The cerebellum was also diffusely pigmented in its
upper layers with the exception of the left cerebellar tonsil
and the flocculi. Slight brownish pigmentation was seen in
the pia mater. The spinal cord was quite free. The other
organs revealed nothing remarkable except the inguinal
lymph glands which on microscopical examination showed
pigment lying in the endothelial cells of the lymph and blood
channels, as well as in the lymphocytes. This was considered
as an absorption of pigment from the skin as described by
Schmorl. As these pigment cells were not found in the
other organs Grahl thinks that it is quite improbable that the
lymphocytes acted as carriers for the pigment. Sections of
the brain taken from those areas containing pigment showed
under the microscope a very marked perivascular infiltration
of cells which were of round, spindle or branching shape.
In the pons this perivascular arrangement was very distinct.
In the cerebellum the pigment cells were almost entirely
localized in the gray matter (granular layer). The pigment
was in the form of fine or coarse round granules but was not
present in all the cells. Grahl calls attention to the forma-
tion of gland-like structures by the pigment cells in the

cerebellum. The ganglionic cells throughout the brain were quite free from pigment. The conclusions that Grahl drew from his case are that the development of the brain and skin nevi are quite independent of each other, and, like Oberndorfer, he disregards any suggestion of metastasis from the skin as accounting for the production of the nevi in brain. He firmly believes that the nevi in both areas (brain and skin) arise from chromophore cells and that these are epithelial in origin. Moreover, Grahl regarded the absence of any destruction of the nervous tissue which lay directly against the pigment cells as well as the normal development of the ganglionic cells as indicating a synchronous development of the pigmented tumor and the nervous tissues of the brain.

As far as we have been able to find the above three cases are the only ones of the kind reported. The fourth, which is our own, we shall now give in detail.

A.V. was a girl two months old from the children's clinic in the Burgerspital, Strassburg, with the clinical diagnosis of gastroenteritis and tracheitis.

The autopsy was done by Dr. Tilp on Oct. 24, 1907. The body was that of a very thin and poorly developed female child fifty-eight centimeters long. Icterus was present. Post-mortem lividity was seen on the front and back of the trunk. Rigor mortis was present only in the legs. The hair was blond and scanty. The pupils were contracted and equal. Over the abdomen there was a marked greenish discoloration. There were four pigmented nevi on the skin surface; one, three centimeters in diameter, was present on the back to the right side of the lower dorsal vertebræ; one, two centimeters across, to the right of the middle line over the sacrum; another in the left anterior axillary line at the level of the fourth rib one and one-half centimeters in diameter and a small pigment spot on the outer side of the right foot half a centimeter square.

The soft tissues covering the skull were pale, and in the parietal region the skull was particularly thin. The anterior fontanelle measured 5 x 4 centimeters. The horizontal circumference of the skull was 36.5 centimeters. The sinuses of the dura contained a dark fluid blood. The pia mater over the cerebellum, pons, and medulla showed a marked thickening, and there was also a considerable sub-pial edema present. There was a very striking black pigmentation to be seen on both surfaces of the cerebellum, pons, right posterior corpus quadrageminum, and on the striated nucleus in the wall of the left lateral ventricle. Congestion and edema was present on the brain.

A cross section of the cerebellum and pons made after hardening the specimen in formalin demonstrated very clearly the location of pigment in this portion of the brain. Practically the whole pons, the greater part of the cerebellar folds and the dentate nuclei (Fig. 5) showed a grayish-black pigmentation. On separating the hemispheres of the cerebrum in the middle line there was also a small pigment nodule one-fourth centimeter square on the median surface of both optic thalami corresponding to the insertion of the commissura media (Fig. 1).

The diaphragm arched to the fourth rib on the right, fifth rib on the left. The trachea and organs of the throat were slightly congested. The lungs were free from adhesions. The cut surface showed some congestion, and in the upper lobe of the right lung some patches of consolidation were seen. The bronchi contained some white mucus. On the pleura of the right lung some brownish red spots of ecchymosis were noted. The thymus was relatively large. The heart was normal. The liver was pale. The spleen was a little enlarged measuring 8 x 4.5 x 2 centimeters. Its cut surface was normal. In the pelvis of the left kidney there was a slight amount of renal sand. The genital tract was normal. There were some slightly enlarged grayish-brown lymph glands in the neighborhood of the hilus of the kidney. The lymph follicles of the large and small bowel were distinctly enlarged and some showed white spots on their surface. Seventy centimeters above the ileo-cecal valve there was a collection of follicles one centimeter in diameter showing an ulcer six millimeters square on the surface. The margins of the ulcer were irregular, and its base was deeply congested. A Meckel's diverticulum ninety centimeters above the ileo-cecal valve was noted. The diverticulum was two centimeters in length. General congestion of the large and small intestines was also present. The mesenteric lymph nodes were slightly enlarged. At the knee joint the markings between cartilage and bone were quite distinct and normal. The medulla of the bone was also normal.

The anatomical diagnosis was as follows: Catarrhus intestinalis acutus; Ulcus catarrhalis ilei; Nephrolithiasis sin; Bronchitis suppurativa; Pneumonia lobul. d.; Nevi pigmentosi cutis; Pigmentatio brunea cerebelli et pontis Varolii; Diverticulum Mekeli simpliciter clausum.

Tissue from the skin nevi, from the cerebellum, pons, and the nodule in one of the optic thalami was given to me by Professor Chiari for special study. (Museum number is 4490.)

Sections were made from the nevi of the skin, from the cerebellum, pons, and the nodule from the optic thalamus. The tissue was embedded in celloidin, and the sections were stained by hematoxylin and eosin which gave much better results than van Gieson's stain or carmine. The sections from the different nevi of the skin showed the same general structure and varied only slightly in minor points. On the

whole, however, they revealed the typical features of the usual nevus pigmentosus of the skin. The epithelial layer covering the nevus was well marked in the nevi from the back. There was no suggestion of a dipping downwards of epithelial processes from the deep layers into the nevus masses lying in the cutis. Immediately under the epithelium was an uninterrupted connective tissue. This layer was very thin, especially where collections of nevus cells tended to compress it against the epithelium, but it could always be made out. In the upper part of the cutis immediately below the connective tissue layer were many round or oval collections of cells most of which contained pigment in the form of fine or coarse granules. These cells were different in size and shape. Many were distinctly stellate while others were round, and occasionally spindle shaped. Some of these cells did not contain pigment. We were unable to demonstrate clearly any connection between these masses and the epithelial cells of the epidermis. Under the pigment containing layer is the main mass of non-pigmented nevus cells. They were so closely packed that it was a very difficult matter to recognize any special arrangement. A definite connective tissue stroma easily brought out with van Gieson's stain was present between the nevus cells. Tiny blood vessels with distinct endothelial linings were quite plentiful throughout the stroma. The nevus cells were round or oval and gave the impression of being decidedly compressed as Ribbert has shown. The nuclei were vesicular and well stained, but very little cell protoplasm could be seen. These cells did not contain pigment. However, scattered among the non-pigmented cells there were a few stellate cells similar to those seen in the upper layers of the cutis, containing free granules of pigment. In the nevus cells we could never distinguish any epithelial characteristics as, for example, intercellular bridges. Nuclear division was not present. Normal hair follicles and sweat glands were present about the tumor masses of all of the sections, but the sebaceous glands were not so well marked.

The sections of the cerebellum (Figs. 2 and 4) were very interesting and showed much better than the skin the type of cell which was responsible for the diffuse pigmentation of the organ. The contrast between the nervous tissue and the pigment bearing cells was very distinct. The cerebellum was covered by a thin layer of embryonal cells which had not at this time disappeared. These small polygonal cells were quite free from pigment. In the granular layer of the cerebellar folds large quantities of a brownish-black pigment were seen. Only here and there could the pigment be found as small isolated masses in the molecular layer of the folds. In the dentate nucleus also the collection of pigment was extremely well marked, but for the rest of the cerebellum it was practically free. Pigment could not be demonstrated in the epithelial cells of the ependyma. The pigment, even with low power, was seen to lie in cells which had a definite perivascular arrangement. This was particularly well marked in the granular layer of the cerebellum and in the pons where one could very clearly make out the endothelial lining of the blood capillaries quite free from pigment, while immediately around the periphery of the capillaries there was a layer of pigment cells. In these areas where the cells were more loosely and irregularly scattered in groups of two or three or singly the perivascular arrangement was often missing, and they appeared as isolated pigment cells in the nervous tissue. This last arrangement was not infrequent in the pigmented dentate nucleus. The pigment cells were round and spindle in shape while some were distinctly branching. Some of the round cells were much smaller, and were frequently devoid of pigment. These cells bore a striking resemblance to the non-pigmented nevus cells of the skin. The non-pigmented cells were indiscriminately mixed with the pigmented forms, as was also noted in the skin. The pigment was in the form of fine and coarse granules, which at times so completely filled the cell that it was impossible to even recognize the nucleus. In the branching or spindle cells the pigment was as a rule in finer granules and here a vesicular nucleus was made out.

The cells of Purkinje and ganglionic cells were everywhere free from this pigment. In fact the cerebellar nervous tissue showed no deviation from the normal. We were unable to find any gland-like structures composed of pigment cells as described by Grahl.

In the pons (Fig. 3) there was a diffuse perivascular infiltration of pigmented and non-pigmented cells. Here the perivascular arrangement was very well marked, and the number of small round non-pigmented cells in many places exceeded the other varieties. As in the cerebellum pigmented and non-pigmented cells were diffusely mixed. The nervous tissue showed no evidence of destruction although there was undoubtedly a diminished amount of nervous tissue due to the large and numerous perivascular pigment cell infiltrations. A layer of pons substance immediately under the ependyma was free. The other types of pigment cells were similar to those described for the cerebellum; the ependymal epithelial cells were also free from pigment.

Section of the pigment nodule in the optic thalamus showed the same type of pigment cells as noted elsewhere in the brain. Here, however, there were very few non-pigmented cells. The cells were, as a rule, of the round type singly arranged or in small groups of two or three. The perivascular arrangement was not marked. The nervous tissue showed nothing of an abnormal character. The infiltration of the pigment cells in this small localized nodule was exactly the same as the diffuse infiltrations seen in the cerebellum and pons.

In the pia mater covering the cerebellum and pons were many round and spindle pigment cells. Some had a distinctly perivascular position while others appeared to lie merely in the loose connective tissue of the pia. The pigment was, as a rule, in coarse granules and the cells could not be differentiated from those seen in the brain. We failed to demonstrate many non-pigmented perivascular cells in the pia although a few were easily recognized. In all sections the iron reaction for blood pigment was negative.

Before entering into any discussion on our case it may be well to consider briefly the important question which is always brought up when dealing with nevi, namely, the origin of the nevus cell. At the present time there is no uniformity of opinion regarding them and in a similar manner contrary views are held concerning the origin and significance of the pigment contained in nevi. To the latter we shall also very briefly refer. The following four theories have been advanced to explain the origin of the nevus cell:

1. Demieville — a proliferation of the endothelial cells in the adventitia of the blood vessels of the cutis.

2. von Recklinghausen — a proliferation of the endothelial cells of the lymph channels.

3. Unna — a proliferation of the epithelial cells in the deep layers of the epidermis.

4. Ribbert — from the chromophores of the cutis which he regards as of mesoblastic origin.

The first theory has been practically discarded. Most of the controversy has been over the second and third, and it is noteworthy that many supporters of these beliefs hold different views among themselves concerning some of the minor points in the development of nevi. Ribbert has many supporters for his theory, but they likewise disagree on some points. The literature on the subject of nevi is very confusing on account of contrary views being held by many authors.

Borst, following the views of v. Recklinghausen, believes that the proliferation of the endothelial cells of the lymph spaces is brought about through the stimulation by the pigment which has been set free from the epithelial cells in the skin, and which has finally wandered into the lymph channels. Ziegler also was a strong supporter of this belief. He held that the nevi should be classed under the lymphangiomata, and to him the proximity of the nevus cell to the deep layers of the skin was by no means a point signifying an epithelial origin. Riecke, Schutz, and others are also of the same opinion as to the endothelial nature of the nevus

cell, but they do not regard the pigment as being the primary factor in the endothelial proliferation.

The epithelial theory of Unna has attracted many followers. According to this view the development of nevi is due to a pinching off of some of the deep cells of the epidermal pigment layer, followed by their continuous growth. According to this theory the pigment is derived from the Malpighian layer of epithelial cells. Some of Unna's followers hold that the nevus cell still retains part of its original epithelial characteristics. Abesser and Migliorine have both found evidence of this in the presence of prickle cells. These last two observers disagree with Kromayer, who although a supporter of the epithelial origin of nevus cells regards the process in a somewhat different light. He believes that the nevus cell is formed by metaplasia from the deep layers of the epidermis and he goes further to say that the stroma of the nevus is derived by a similar metaplastic process from the nevus cell. Judalewitsch accepts the idea of metaplasia, and points out a definite relation of the pigment content of the cells to this process. In the early stages of metaplasia the pigment is present, but gradually disappears as the nevus cell develops and, therefore, he regards the pigmentation of the superficial layers of the nevus with non-pigmentation of the deep layers as confirmatory evidence of his view. However, as we shall indicate later, a very different interpretation can be given for this. Fick considers that the epidermal origin is undoubtedly confirmed. The proliferation of the deep epithelial cells is according to Ravogli brought about by free pigment from the epithelial cells acting as a stimulus in a way analogous to that mentioned by Borst only on a different type of cell. The epithelial cells settle in the cutis which enfolds them forming a somewhat alveolar structure. The stroma of the nevus, he states, is merely the connective tissue of the part.

Between these two sides there is another group of observers who take an intermediate stand. They do not believe that all nevi have the same origin, and that it is possible for some to arise from endothelium while others may develop

from epithelium. Kaufmann supports this view and considers that it accounts for the wide diversity of opinion on this question. Frederic, although leaning towards the endothelial theory, also takes this stand. Herxheimer, Moeller, and others are inclined to the same belief.

The last theory to mention is that of Ribbert. He considers the nevus cell a derivative of the chromophore of the cutis and moreover he has shown that in freshly teased out material from a nevus the so-called nevus cell assumes a definitely spindle or branching form. In sections this appearance is not noted, due, in all probability, to the fact that the cells are closely packed together and, therefore, tend to take on a more polygonal shape. One not infrequently sees the same condition in tumors where a very dense fibrous stroma develops or where the tumor cells are closely packed together. The chromophores of the cutis, according to Ribbert, may or may not contain pigment. The majority of them do. The nevus cells are notoriously free from pigment, and Ribbert regards them as representing immature forms of chromophore cells which never reach the stage of pigment production. To further follow Ribbert's theory the question is naturally asked whether the chromophore cells are epiblastic or mesoblastic in origin. It is upon this point that his adherents are divided. Ribbert himself adheres to the mesoblastic origin while Marchand, Lubarsch, and others take the opposite view. In his review of the subject Adami, although in favor of the mesoblastic origin of the chromophores, states that the question is not as yet settled. According to him, however, the work of Stoffel and Maximow helps a great deal to prove the mesoblastic theory. In a study of perivascular cells in the lymph spaces Stoffel was able to show numerous variations in the form of the cells ranging from a typical lymphocyte on one hand to a branching spindle cell containing pigment on the other. These branching forms Stoffel regarded as being but modified lymphocytes. In a similar work Maximow has also definitely shown spindle and branching cells in the perivascular spaces which he considered derivatives of plasma cells. The fact

that nevi and chromophore cells are prone to assume a perivascular arrangement in the tissues is according to Adami a very suggestive point in favor of the mesoblastic origin especially when associated with the studies of Maximow and Stoffel.

The occurrence of chromophore cells in the pia mater with particular reference to the region of the medulla oblongata has been investigated by Broniatowski. He found that branching cells containing pigment first appeared about the ninth year of life. Previous to this age spindle and branching cells are found, but they do not contain pigment. He regarded them, however, as non-pigmented chromophores. As age advances the pigment becomes darker. The cells are, as a rule, perivascular, but they also exist free in the loose connective tissue of the pia. According to Broniatowski, pigment bearing chromophores in the pia are physiological after the ninth year of life either in fair or dark individuals. Somewhat associated with this is what we can term a pathological development of the chromophores of the pia as seen in primary melanotic sarcoma of the pia mater. There have been several cases reported, and recently the subject has been reviewed and a new case added by Schopper. This was a very diffuse pigmented sarcoma of the pia mater in a woman of fifty-nine, which involved the pia of the spinal cord and base of the brain. The growth was primary in the pia mater. Microscopically the tumor consisted of spindle and branching cells which had a very marked perivascular arrangement. Some of the cells contained pigment, while others were free. Schopper believed that the tumor arose from the chromophores of the pia mater. In other similar cases of primary melanotic sarcoma of that tissue the same perivascular arrangement was always noted, but occasionally the majority of the cells were round instead of being spindle shaped or branching. All of these malignant melanomas occurred in adults.

The production of pigment in the chromophore cells we shall but briefly mention. This question at the present time has become so involved that it can only be set aright by the

physiological chemist. Many believed that the red blood was primarily responsible for the pigment seen in the chromophores. Aeby and Ehrmann were exponents of this view. However, on chemical analysis the pigment (melanin) differed considerably from blood pigment. The iron reaction was usually absent, and a relatively large quantity of sulphur was present. Both of these points are against a blood origin. At the present time the most accepted view is that of von Furth, who considers that melanin is produced by the action of an intracellular oxidase on the chromogen radical of the proteid molecule (Adami).

In considering the essential features of our case, the similarity between it and those reported by Rokitansky, Oberndorfer, and Grahl is indeed very striking. More particularly is this true of the last two mentioned. The almost symmetrical arrangement of the pigment deposition in the brain suggests some common anatomical factor about which at the present time we are quite in the dark. With Oberndorfer and Grahl we agree that the cases illustrate the development of pigmented nevi occurring independently in the skin and the brain. The nevi in the brain are in no sense metastases from the skin but are benign tumors arising primarily in the brain. The condition in the pons and cerebellum could rightly be called nevus pigmentosus diffusus.

The origin of the nevi according to Oberndorfer and Grahl is from the chromophores, which in the brain arise from the neuro-epithelium and in the skin from the epidermis. In part we agree with these authors, namely, in that the nevi are developed from chromophore cells, but we do not believe that these cells are of epithelial origin. In our sections of the brain there were three outstanding features regarding the pigment cells. Firstly, the cells varied in shape from round to spindle or branching forms; secondly, many of the round forms were free from pigment while practically all the spindle and branching forms contained pigment; thirdly, the cells, as a rule, assumed a decided perivascular arrangement. These points also hold true for

the nevi of the skin except that the perivascular arrangement is not so apparent on account of the close arrangement of the cells. Comparing our finding with the works of Maximow, Stoffel, and Broniatowski leads us to believe that the chromophore theory of Ribbert is correct. This theory, as we have previously indicated, regards the non-pigmented nevus cell as being but an immature form of the chromophore which never reaches the stage of producing or containing pigment. The appearance of perivascular cells according to different authors varies greatly from round to spindle and branching forms which at times are known to contain pigment. These cells are mesoblastic in origin. Also in studies pertaining to chromophore cells in the pia mater certain characteristic points are brought out which correspond very nicely with the work on perivascular cells. Broniatowski has shown that chromophores in the pia vary in size, shape, in their pigment content, and have a definite perivascular arrangement. In a similar way do the characteristic points of the cases reported by Oberndorfer, Grahl and myself agree. It is especially interesting in Schopper's studies to find a melanotic sarcoma arising primarily from the chromophores of the pia mater with round, spindle, and branching cells, some with, others without, pigment. As a rule, these cells were shown to have a marked perivascular arrangement. In respect to the question of the relation of such nevi in the brain to the development of sarcoma we believe it to be quite analogous to the relationship of cutaneous melanosarcoma and nevi pigmentosi of the skin. The development of the nervous tissue of the brain and the nevi apparently progresses independently without, and as far as one can observe any direct injury to the brain substance.

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DESCRIPTION OF PLATE XXII.

FIG. 1. — Pigmented nevus in optic thalami and floor of fourth ventricle.

FIG. 2. — Diffuse pigmented nevus in the granular layer of the cerebellum (low power).

FIG. 3. — Perivascular arrangement of the nevus cells in pons. The majority of the cells are free from pigment (low power).

FIG. 4. — Pigmented nevus cells in cerebellum; these cells have round, pindle, or branching characters (high power).

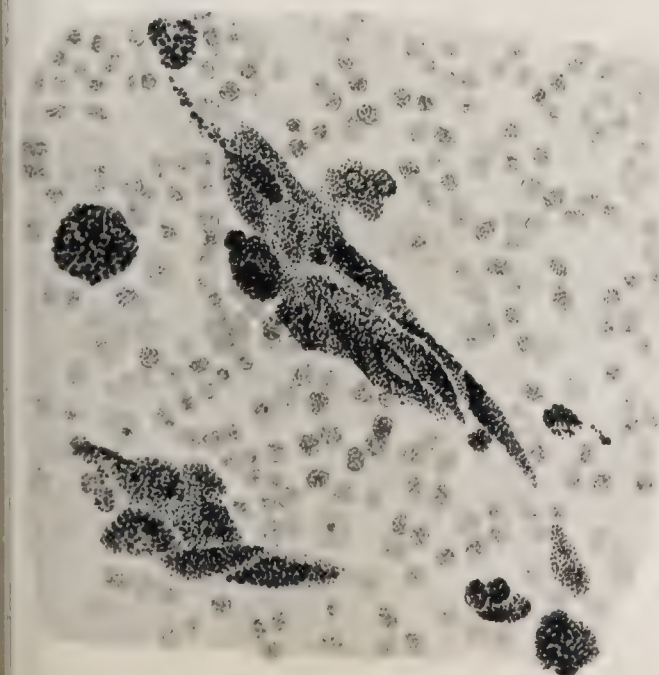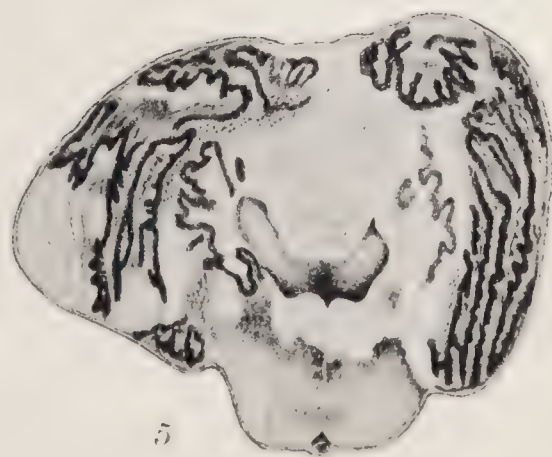FIG. 5. — Cross section of the pons and cerebellum showing situation of pigmented nevus.
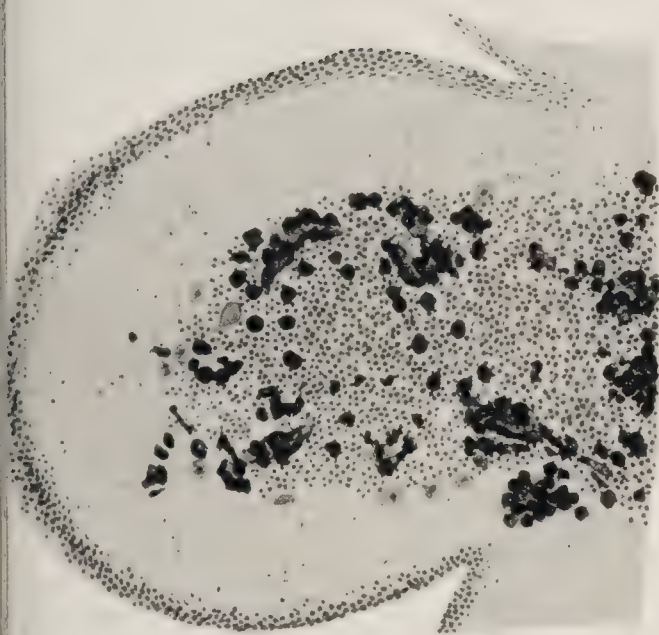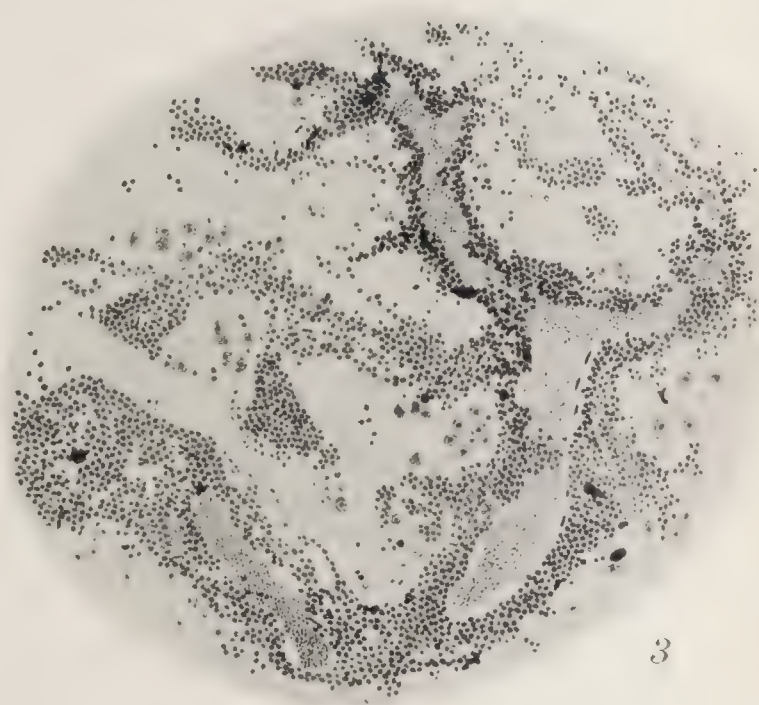
PURPURA ASSOCIATED WITH BACIL-
LUS MUCOSUS IN THE BLOOD

G. C. WEIL

AND

J. W. McMEANS

PURPURA ASSOCIATED WITH BACILLUS MUCOSUS IN THE BLOOD

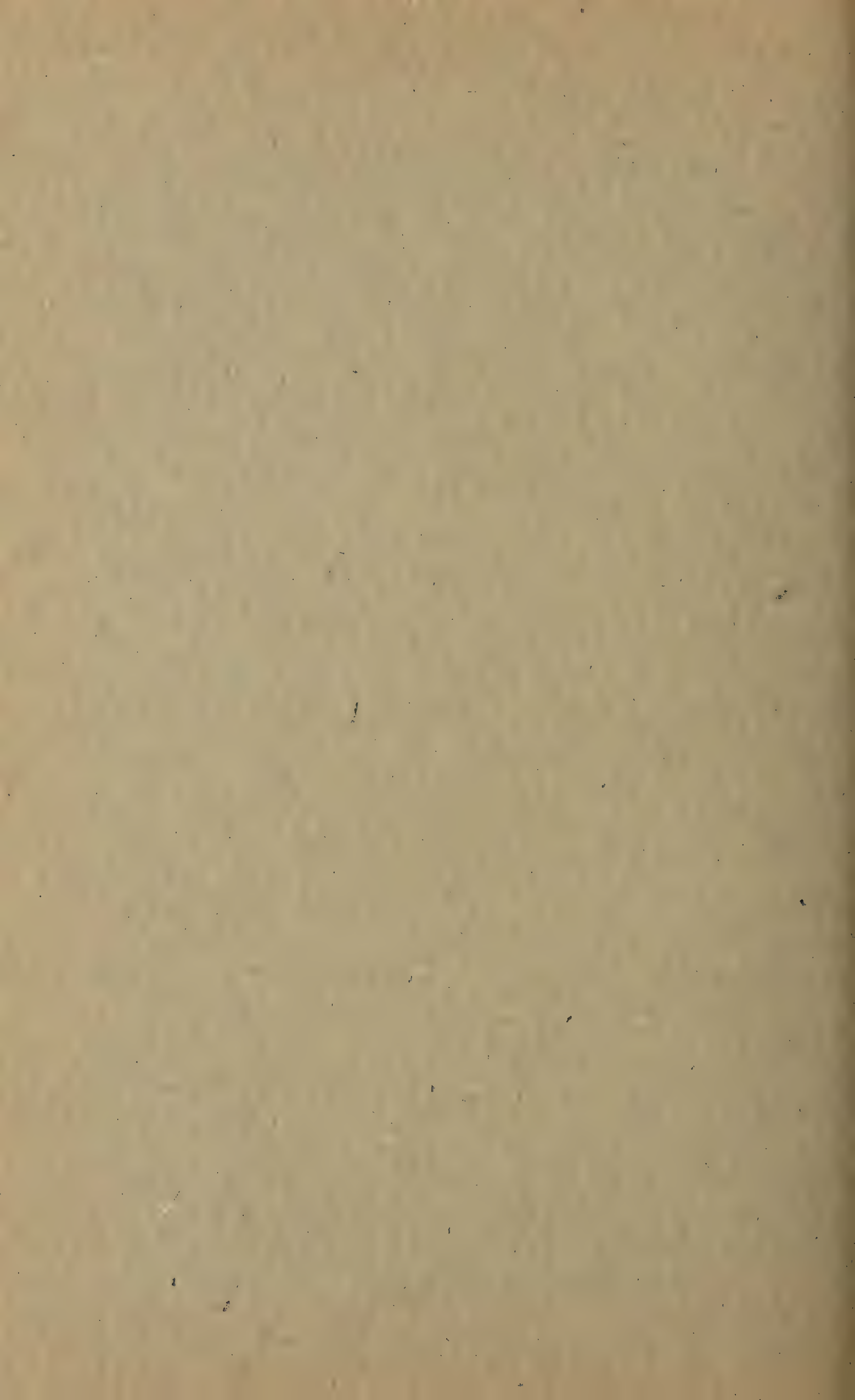G. C. Weil and J. W. McMeans

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Reports of bacteriemia due to members of the bacillus mucosus group of organisms, in which the diagnosis has been verified by blood-culture during life, are comparatively infrequent in the literature. At autopsy, however, cultures have been reported quite frequently in which the evidence was in favor of such infection. In the case here reported capsulated bacilli were twice recovered from the blood and the urine during life, as well as from the heart's blood, various organs, and urine at autopsy. Our case is also of interest in its clinical course, the development of the blood infection from the urethra and the late onset of the purpura.

The term bacillus mucosus capsulatus employed by Fricke for the group of bacteria here referred to, is the one which we prefer rather than bacillus pneumoniae (Friedländer), since the former is descriptive of one of the characteristics common to all the members of the group, is indicative of no particular disease, and is broad enough to include the many Gram-negative capsulated bacilli which show common biological and cultural characters. There has been and still is confusion in the nomenclature, as shown by the long list of names applied to bacteria, which undoubtedly are members of the mucosus group. The general characteristics of the group are as follows: The bacilli occur as short plump rods, singly or in pairs, often coccoid, while long and even thread-like forms may develop and under certain circumstances fairly long chains occur. No spores are formed. Motility is not observed. Capsules are produced in most media, the addition of serum favoring their development. Growth is luxuriant on all media, aerobic conditions being more favorable than anaerobic. A mucus-like substance is formed in the cultures. Coagulated serum, casein and gelatin are not liquefied. Indol is generally not formed in peptone solution. Fermentation to acid and gas of certain carbohydrates is characteristic of the group, the members differing in the carbohydrates they attack,

and in the degree of fermentation. Marked tenacity of life is exhibited under ordinary conditions.

Pathogenicity for man and the laboratory animals is somewhat variable, but usually present.

In the classification of the organisms belonging to this group we have found that all the Gram-negative capsulated bacilli, which we have obtained in the laboratory from a variety of sources, come under one or the other of three types, as described by Perkins[1] and others.

This led us to adopt the following practical classification, based on the fermentation of certain carbohydrates: (1) The bacillus lactis aërogenes (Escherich), which possesses the most marked power of fermentation, producing acid and large amounts of gas in dextrose, lactose and saccharose broth. It has been our experience to find this member most frequently. (2) The bacillus acidi lactici (the bacillus duodenale of Ford[2]) possesses in a lesser degree the power of fermentation. It produces acid and gas in dextrose and lactose broth, but fails to attack saccharose. It produces very much less gas than the bacillus lactis aërogenes. (3) The bacillus pneumoniae (Friedländer) ferments dextrose and saccharose to acid and a small amount of gas. In our experience these organisms, when thoroughly studied, produce a late and slight fermentation of lactose. Litmus milk is not coagulated. This micro-organism is found much less frequently than either of the other forms.

The difficulties which have arisen in establishing a classification of the members of the mucosus group can, in a great measure, be traced to incomplete examination, and the failure to recognize the fact that organisms which have the ability to ferment carbohydrates may lose the power in whole or in part through changes in environment or unfavorable conditions (Perkins[3]). The fermentation reactions are no more variable than in the bacillus coli recently isolated from water. In making this classification we would not exclude those indefinite organisms reported in the literature, but we would state that they belong, in all probability, to the degenerated or other types referred to.

As a cause of disease, the capsulated Gram-negative bacilli have been recognized in a great variety of pathological conditions, the discussion of which, at this time, would lead us too far afield and we would rather confine our remarks to those points which chiefly concern the

1. *Jour. Infect. Dis.*, 1907, 4, p. 951.
2. *Stud. Roy. Victoria Hos., Montreal*, 1903, p. 1.
3. *Jour. Infect. Dis.*, 1907, 4, p. 951.

case reported in this paper. However, we would here call attention to the occurrence of Gram-negative capsulated bacilli in conditions involving the respirating tract, accessory sinuses, middle-ear, gastro-intestinal tract and not infrequently the genito-urinary tract.

In reviewing the literature we find that the presence of a definite bacteriemia due to the bacillus mucosus is comparatively rare. Wolff[1] was able to collect from all available literature prior to 1909, 39 cases, the organism recovered being referred to as the bacillus pneumoniae (Friedländer). In 11 of these cases the organism was recovered from blood before death. In the remaining cases, however, he states that the clinical and pathologic picture before death was so definite that they might be classified with the cases of true bacteriemia without comment. Nineteen of the 39 cases had their primary focus in the lung, 17 were of cryptogenic origin, 5 arose in the liver and gall ducts, 5 came from the urogenital tract, 2 from otitis media, and 1 from a phagedenic ulcer. In 13 of the 39 cases, metastases were found in the liver (5 times), in the kidney (4 times), in joints (3 times), in the ear (2 times), in the thigh (1), and in the sternocleidomastoid muscle (1). Two of the above cases recovered.

Hirschbrook and Ziemann[5] report a fatal case in which the bacillus lactis aërogenes was isolated at autopsy from the heart's blood and different viscera. Owing to the clinical manifestations and the recovery of the bacillus typhosus from the stools, this case was first looked on as one of ordinary typhoid fever. Subsequently, however, the symptoms became very acute with the development of purpuric spots and a second examination of stools failed to show presence of the bacillus lactis aërogenes widely disseminated in the body. Diffuse petechial hemorrhages were present. From the results of examination after death it was maintained that the condition was one of the bacillus mucosus capsulatus bacteriemia developing secondarily to typhoid.

Closely associated with the systemic infection by the bacillus mucosus is the development of petechial hemorrhages, not only on the skin surfaces, but also in various viscera, and on the lining membranes of the body cavities. In a review of 10 cases, Abel and Hallwacks[6] showed the frequency of occurrence of hemorrhagic purpura associated with the bacillus mucosus in the blood. From the literature we have found that the petechial hemorrhages seem to arise at the time when the patient is overwhelmed with infection, 5 or 7 days prior to death. These hemorrhages make their appearance as an erythematous rash, later developing a more bluish and finally a deep cyanotic character.

It has not infrequently been found that the bacteriemia due to the bacillus mucosus has originated from the genito-urinary tract. Chiari has reported a case of ascending infection of the genito-urinary tract which at autopsy showed cystitis, prostatic and renal abscesses, endocarditis, infarct of the spleen, and purulent meningitis. Howard[7] has also reported a case of bacteriemia arising from the genito-urinary tract showing chronic cystitis, renal abscess, and peritonitis. It is worthy of note that localized infections simulating chronic gleet may result from an infection by the capsulated Gram-negative bacilli. A case of chronic urethritis reported by Avery,[8] and another with urinary fistula from which

4. Beiträge zur Pathologie der durch den Bazillus Friedländer erzeugten Sepsis, Dissertation, Leipsic, 1909.
5. *Cent. f. Bakteriol., orig.*, Abt. 1, 1913, 70, p. 281.
6. Kolle and Wassermann, *Handb. d. Path. Mikroorg.*, 1913, 6, p. 515.
7. *Jour. Exper. Med.*, 1899, 4, p. 149.
8. Standard Methods of Water Analysis, 1912, p. 84.

the organisms isolated had characters of the type of the bacillus lactis aërogenes was reported by White.[9] Bernstein isolated capsulated Gram-negative bacilli from an acute epididymitis, and also from a purulent orchitis. Schenk and Weltman isolated capsulated Gram-negative bacilli from the inflamed fallopian tubes. Allen[10] reported a case of gleet due to the bacillus pneumoniae (Friedländer) which, when treated by autogeneous vaccine, was followed by a satisfactory recovery. As an etiologic factor of inflammatory processes in man we find that the bacillus lactis aërogenes had been most frequently isolated.

Heyse,[11] Wildholz[12] and Schnitzer[13] each reported a case of pneumaturia due to the bacillus lactis aërogenes, while Trumpp[14] found one such infection in 29 cases of cystitis in children. In none of these cases did a generalized infection occur, but the symptoms were at times quite severe.

Recently Leutscher[15] reported 2 cases of the bacillus lactis aërogenes infection of the bladder and commented on the infrequent presence of the organism as a cause of cystitis. His cases are interesting. In the first, a woman developed cystitis during the second month of pregnancy and subsequently infected her husband. Both suffered urethritis and cystitis from which the bacillus lactis aërogenes was isolated.

The case which we desire to report was an Italian of 42 years. He was admitted to the Mercy Hospital, April 1, 1913, under the service of Dr. J. P. Griffith. He complained chiefly of painful, frequent, and difficult urination. He stated that the present illness began Jan. 24, 1913, when he suffered a severe chill as well as some bladder distress. He was treated by a physician, and sounds were passed into the urethra. His chills then became periodic, recurring once or twice a week. The patient always recovered completely from effects of each chill and he was able to go about during the intervals.

The patient was slightly emaciated and rather anemic. Considerable tenderness over the left lobe of prostate with slight enlargement. The passage of sounds showed an obstruction in the posterior urethra.

The patient had had the usual diseases of childhood and recovered without complications. He suffered an attack of malaria at 19 years and an attack of pneumonia at 32 years. He had been married 15 years and migrated to America 5 years ago. He developed gonorrhea 20 years ago, which continued in a chronic state many years. Ten years ago he claimed to have had a condition similar to the present from which he fully recovered.

The circulatory, respiratory, and digestive systems appeared normal. The urine showed the presence of a slight amount of albumen and some leukocytes. Gonococci could not be demonstrated.

April 3.—Two hours after first passage of sounds, the patient suffered a severe chill and fever, temperature 105.4 F. The patient remained in bed the following day and appeared quite well. Temperature and pulse normal.

April 9.—Eight days after admission the stricture was forcibly dilated under anesthesia, which was followed in a few hours by a severe chill and high fever, 105.6 F. The following day the patient was again sufficiently well to leave his bed.

9. *Ibid.*
10. *Vaccine Therapy*, 1910, p. 127.
11. *Ztschr. f. klin. Med., Berl.*, 1894, 24, p. 130.
12. *Cor.-Bl. f. schweiz. Aerzte*, 1901, 21, p. 683.
13. *Internat. Klin. Rundschau*, 1894, 8, p. 265.
14. *München. med. Wchnschr.*, 1896, 43, p. 1008.
15. *Bull. Johns Hopkins Hosp.*, 1911, 22, p. 360.

April 17.—Sounds were again passed and the patient again suffered a severe chill, with a fever of 103.4 F., from which he fully recovered on the following day. The urethra at this time was quite patent and permitted the passage of a 28 F. sound. Examination of urine at this time showed a slight amount of albumen with a few leukocytes, while in culture the bacillus lactis aërogenes was isolated.

Following the chill on April 17, the patient recovered except for a general muscular soreness and several painful points, especially about the limbs and shoulders. The patient had been receiving ordinary urinary antiseptics. On May 3 he complained of a burning sensation in the bladder and penis, especially during urination.

May 15.—Sounds were again passed into the urethra. No evidence of stricture was found at this time. Shortly following the passage of sounds (37 F.) the patient suffered severe chills and fever of 104.6 F. From this date on the temperature persisted with frequent chills and fever. The patient's general condition was not greatly affected, save for great lassitude.

May 22.—Following another chill a blood culture was taken. The bacillus lactis aërogenes was isolated.

Blood examination:

Hemoglobin	70 per cent.	Polynuclears	87 per cent.
Red cells	4,098,000	Eosinophils	1 per cent.
Leukocytes	68,000	Large lymphocytes	3 per cent.
		Small lymphocytes	8 per cent.
		Transitional forms	1 per cent.

May 26.—Since last passage of sounds the patient had a septic temperature with frequent chills; appetite greatly impaired and evidence of emaciation and anemia appearing; pains in limbs and continuous sharp pain over precordium, but examination of chest and heart showed no lesion.

The high temperature continued, the pulse of good volume, not above 120. The chest wall showed petechial hemorrhages, hip and limbs a mottled erythematous condition.

May 29.—Examination of prostate revealed a great tenderness, but only slight enlargement. After thoroughly cleansing urethra, a culture of the bacillus lactis was obtained of the prostatic secretion by massaging the posterior urethra.

May 30.—The general condition was quite alarming, with vomiting for past few days.

May 31.—The temperature was still very high; intense burning and dryness in the throat. A catheterized specimen of urine gave a pure culture of the bacillus lactis aërogenes. Hemorrhagic spots became darker and more diffuse. There was a slight amount of albumen in urine, but no leukocytes. Red cells, 3,870,000; hemoglobin, 65 per cent; leukocytes, 9,700.

June 1.—Blood culture was found to contain the bacillus lactis aërogenes.

June 6.—For three days the patient appeared very toxic and although rational, he was very nervous. Pain in the chest was intense and continuous. He was unable to swallow much food but had an intense thirst. His temperature was high, but the pulse was not above 130 per minute; the skin showed a diffuse mottling of petechial hemorrhages considerably darker and more bluish than when first observed.

June 7.—Death.

It is evident that we were dealing with an infection due to the bacillus lactis aërogenes. Blood cultures on two different days gave a pure growth of the bacillus lactis aërogenes. The cultures were made in 1 per cent. dextrose serum broth and at the end of 24 hours the blood clot was blown up, floating in the medium with many white vertical, candle-like growths.

Cultures of the bacillus lactis aërogenes were also recovered from the prostatic urethra and the urine. From the bacteriologic evidence the genito-urinary tract appeared to be the point of entrance for the development of the bacteriemia.

Autopsy twenty-four hours after death (Dr. O. Klotz.)—The surface of the body rather pale, the face yellowish, the teeth poor, mucous membranes pale. Over the neck, chest, abdomen, thighs and arms was a diffuse purpuric rash, which, for the most, was pinhead in size, but which occasionally showed small hemorrhagic blotches, the largest 1.2 cm. in diameter. The face, hands, and legs below the knees, showed none of these spots. The rash was also seen on the back where postmortem lividity was well developed.

There was a single old adhesion near the apex of the left lung and some diffuse adhesions over the diaphragmatic surface of the right lung. The pericardium contained about 150 c.c. of turbid fluid with many lymph flakes; the surface dull and granular with a single calcareous nodule near the apex of the left lung. The heart weighed 550 G. The right ventricle was large; projecting into its upper part just below the pulmonary valve and lying behind the insertion of the tricuspid valves on the septum was a mass, 4 cm. in diameter, the muscle over it of a yellow necrotic color with hemorrhages; the muscle of the right ventricle otherwise pale and cloudy. The pulmonary and tricuspid valves normal. Throughout the muscle of the left ventricle many yellow spots with hemorrhagic streaks or dots. The papillary muscles showed yellow mottling. The coronary arteries over the surface of the left ventricle very prominent, with definite chains of little nodules in some of them. The mitral valve quite healthy, save for a single, small deposit of recent fibrin. The aortic orifice over half its extent obliterated by a massive thrombotic deposit resting on the heart muscle and the aortic valve in front of the posterior coronary artery filling the corresponding sinus; this mass, which completely obliterated half of each of the adjoining valves at this point, was the size of a small walnut. The vegetation rested on that portion of the heart muscle which was observed to project into the right ventricle. The myocardium just below the aortic ring was much thickened and appeared partly necrotic; in cutting it a small necrotic cavity or abscess was entered; the posterior coronary artery passed over the outside of this mass and was so compressed that its lumen was all but obliterated. When more closely examined, the mass was found to occupy a saccular dilatation of the lower portion of the posterior sinus of Valsalva which projected into the musculature of the septum and posterior parietes so that a protrusion had taken place into the septum and right ventricle.

The base of the aorta quite smooth and elastic, nodular plaques in the thoracic and abdominal portions.

The peritoneum, mesentery, and omentum dotted by small petechial hemorrhages, the majority of which were the size of a pinhead.

The gastric mucosa showed numerous petechial hemorrhages and near the pyloric ring were a number of the marked erosions of the surface.

Here and there in the small and large bowel submucosal hemorrhages were observed, at times 1 cm. in diameter.

Along the upper and anterior border of the spleen, which was large, was a yellow area 2.5 cm. in width, with a dark red center which extended into the organ as an infarct; the spleen substance easily broken, dark in color,

The kidneys large, capsule peeled readily; on the surface many small gray areas about the size of a pinhead; in the left kidney one larger yellow area surrounded by hemorrhagic zone; the cortex and medulla not well defined; the small gray dots observed on the cortex seen as fine gray lines on the cut surface.

The bladder small, walls somewhat thick, the mucous membrane everywhere dotted with bright red hemorrhages, the majority of which were of pinhead size. The prostate not enlarged, but showed some small purulent areas in its substance.

The principle results of the microscopic examination may be summarized by saying that there was a chronic and acute myocarditis and suppurative nephritis.

Culture from the heart blood, from the abscess in heart, from the pericardium, bile, contents of small intestines, and from the bladder, all gave the bacillus mucosus. From the abscess in the heart there was isolated also the micrococcus tetragenus.

Anatomical Diagnosis.—The bacillus mucosus capsulatus bacteriemia; infectious purpura; acute vegetative aortic, mitral and mural endocarditis, acute mycotic aneurysm of sinus of Valsalva, stenosis of aortic orifice; acute purulent myocarditis; hypertrophy and dilatation of the heart; acute serofibrinous pericarditis; chronic interstitial myocarditis; petechial hemorrhages of skin, pleura, pericardium, stomach, intestines, peritoneum, pelvis of kidney, ureter, and bladder; acute splenitis; splenic infarct; infarcts and multiple abscesses of kidneys; acute purulent prostatitis.

The organisms isolated from the blood, urine, and prostatic secretion before death and those from the blood and various organs at postmortem were carefully studied. They all showed the following characteristics: They appeared mostly in the form of short plump rods with rounded ends, although in some of the older cultures irregularly sized bacilli were seen forming long and short threads. From the milk agar plates, chains of short capsulated diplobacilli were seen. The bacilli were non-motile, definitely Gram-negative, and did not form spores. Capsules were easily demonstrated from the litmus milk and other media.

In plain broth at the end of twenty-four hours there was a slight cloud, which gradually increased, the broth becoming quite milky in appearance with a heavy white gummy sediment and the development of a thin shiny pellicle especially around the edges, forming a ring on the wall of the test tube. There was no odor.

Plain agar slant showed a shiny, luxuriant, well-defined streak at the end of twenty-four hours. This growth later became heaped up and porcelain-white in color, mucoid, watery, with the growth running down to the bottom. It was very viscous, drawing out in long strings with the platinum needle.

In gelatin stab cultures, the organism grew in a spreading white film on the surface, which did not become heaped up but remained quite flat. Along the line of the stab, fine granules were formed which later ran together and formed a compact streak. After considerable time there appeared fine outgrowths from the stab and the gelatin along the stab became quite cloudy. The gelatin was not liquefied and there was no browning after three months.

On potato slant the growth was shiny, cream colored, sticky and showed much gas production. The growth, after two weeks, became pale yellow.

There was no indol formed after four days in Dunham's peptone solution, tested by Ehrlich's paradimethylamidobenzaldehyde test.

Cultures on litmus milk showed marked acidity in twenty-four hours. On the second day there was firm coagulation with later reduction of the litmus, the clot separating from the clear whey. Capsules easily stained by Welch's method.

Dextrose, lactose, saccharose, mannite, and raffinose broths showed fermentation to acid and much gas in twenty-four hours. At the end of two weeks there was complete decolorization of the fuchsin indicator with absorption of a varying amount of the gas. Dulcite was not attacked. Potato starch broth showed gas production, as did also deep potato starch agar.

On litmus milk agar plates (at the end of twenty-four hours) a spreading watery growth developed which ran down on the cover of the Petri dish. When it was lifted off, long strings of the mucoid growths were formed. At the end of twenty-four hours the medium was pale pink, and in several days the reaction became distinctly alkaline. This reaction was limited to the region of the colonies.

The organism is undoubtedly the bacillus lactis aërogenes of the mucosus group. We were unable to list it under the classification in "Standard Methods for Water Analysis."

SUMMARY

Clinically, the case was a progressively severe bacteriemia in which cultures of the bacillus lactis aërogenes were obtained during life from the blood, urine and prostatic secretion.
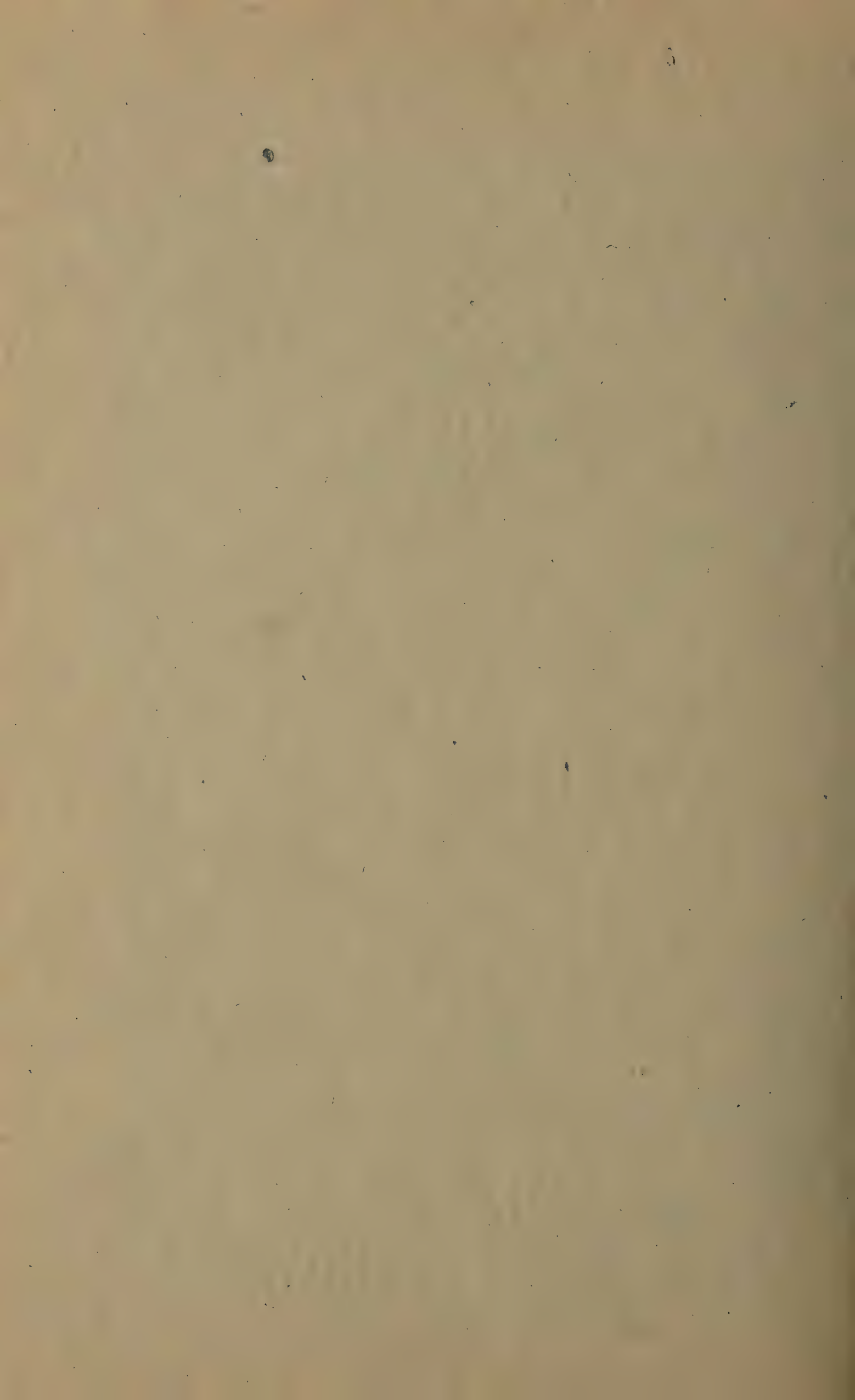
Purpura, although a late manifestation, was the result of this infection.

On account of the systemic reactions after each surgical interference of the urethra, we feel convinced that this was the point of entrance of the infection into the blood-stream.

Probably infection of the genito-urinary tract by bacteria of the mucosus group is more common than realized.

FATTY CONCRETIONS IN
OVARIAN DERMOIDS

BY

J. W. McMEANS, M. D.
Pittsburgh, Pa.

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(With one illustration.)

THE consideration of dermoid cysts and their contents is a very interesting and, at times, a rather perplexing subject. Perplexing in the fact that the nature of the material within the dermoid is at times very different and may be found aggregated into small ball-like masses, each ball being separate and not tending to adhere to its fellows. The occurrence of these individual balls has been difficult of explanation and, at present, there is little definite information on the subject. Thus the reason for the development of the peculiar structures within the cyst is still an open question and remains to be finally settled.

The purpose of this paper is the discussion of one of these peculiar types of dermoid cysts, and to offer, if possible, an explanation for the occurrence of the concretions in the case at hand.

Patient, Mrs. C. R., aged forty-nine years, believed that her present condition of ill-health began about four years after a miscarriage thirty years ago. At this time, she was curetted. She suffered repeated attacks of sharp and severe pain in the right flank which radiated up her side. In January, 1911, the pain became more severe and, in addition to an asthmatic condition becoming worse, necessitated her going to bed. The pain still continued, usually beginning in the right leg and radiating over the abdomen to the right chest. Her last menstruation was very profuse. She had no leucorrhea. She suffered general bearing down pains and backache with frequent desire to urinate.

At operation (May 12, 1911) an ovarian cyst on the right side was removed. The pedicle of the cyst showed a torsion.

Description of Cyst.—The specimen which was received consisted of an ovarian mass with its Fallopian tube attached. The ovary was large, measuring 20 centimeters in diameter. The walls were externally smooth, but on palpation gave the sensation of irregular thickened areas. The color of the serosa was a milky white, with here and there dark areas of congestion. The surface of the cyst showed many large vessels which radiated from the base of the mass. Through the wall of the cyst a number of small spherical bodies could be felt. When

opened, the cyst was seen to contain innumerable putty-like concretions, ranging in size from a pea to a marble, and several larger masses of the same consistence, in which were incorporated many dark brown hairs. The surface of the smaller masses was smooth and of a uniform yellowish-gray color. Many of the concretions showed flat surfaces or facets due to their close apposition to others as they completely filled the cyst. There was no free fluid in the cyst. On section the cut surface of the balls had a homogeneous greasy appearance
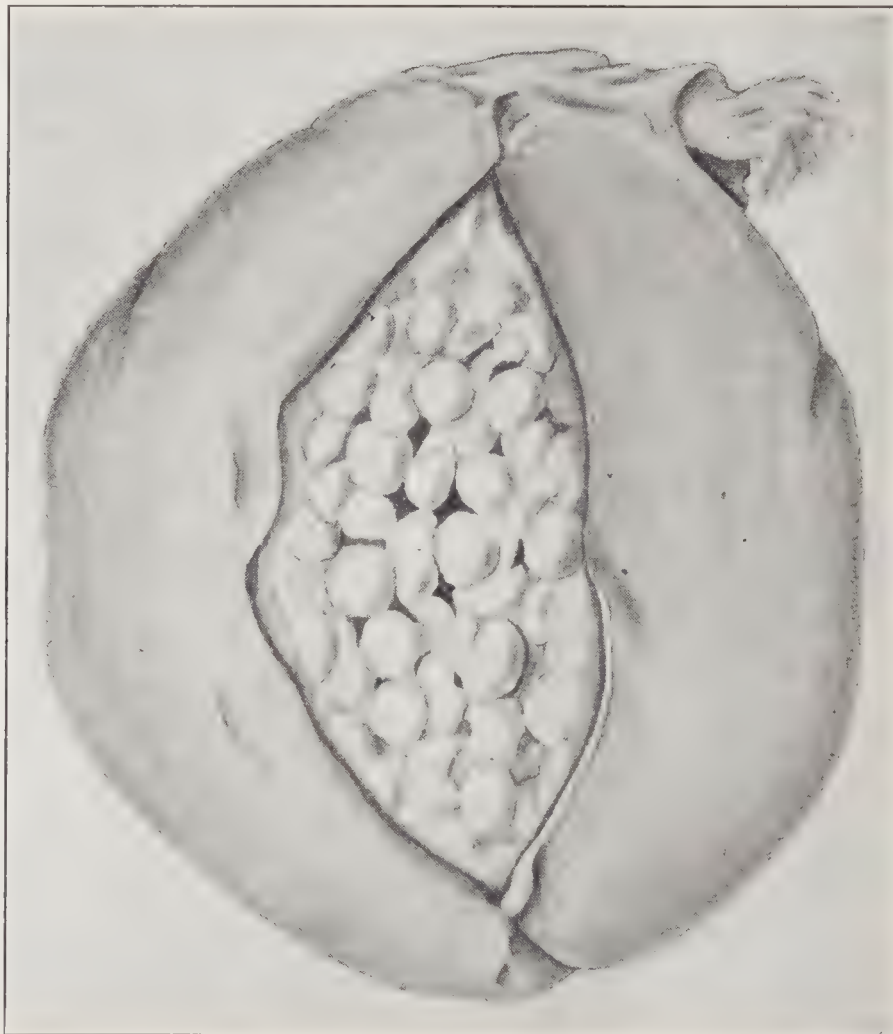

Fig. 1.—Dermoid Cyst with fatty concretions.

with a central irregular cleft, in which was seen a clear brown oily fluid. On section the large masses did not show this central structure but a central core in which many hairs were matted together. The lining of the cyst wall was smooth. The wall showed a number of thickened areas, several of which were quite pale and of a pearly character, while others were of a dark slate color. The cut surface of these areas had a homogeneous cartilaginous appearance.

Microscopical sections of the wall of the cyst showed a structure which was rather loose in places while in others it was quite compact and firm. In places there was an extensive infiltration of red blood cells which replaced considerable areas of the tissue while a large num-

ber of firm-walled and dilated blood-vessels were also present. The tissues of the wall were especially loose in the inner layers where there were seen large pale areas of edema. The wall in its middle and outer third was more firm and here the blood spaces were more abundant. The lining membrane varied in its picture, presenting in places a rather thick layer in which there were seen cells without nuclei, while in other places, the lining was thinner and made up of cells with deep staining oval nuclei. The cells in both instances had a stratified arrangement and were of polygonal character. The superficial layers of the lining membrane showed keratinization and in places, especially where the cells had no nuclei, desquamation of cells could be seen. In places the inner surface of the cyst wall showed no evidence of epithelial lining. Here the surface was covered by a granular amorphous débris which extended for some distance into the wall. Where the lining cells were distinct, a definite supporting membrane was present. Scattered through the wall, and particularly in the epithelial tissues of the lining membrane, there was a diffuse infiltration of inflammatory cells. These consisted for the most part of polynuclear leukocytes and plasma cells, although a number of large endothelial-like cells were also present. This reaction approached the inner surface, especially in those places where the wall was devoid of a lining membrane, and here the inflammatory cells were seen scattered through the granular débris occupying the surface. Other sections of the wall showed, in the deeper layers of the sub-epithelial connective tissue, hair follicles and sebaceous glands. In the immediate vicinity of these structures the inflammatory reaction was not as intense as that in other parts. In these same sections there was seen on the surface a considerable amount of homogeneous pink-staining granular material, some of which was present in the sebaceous glands. Scattered through the middle third of the wall were seen small bundles of muscle cells which were packed between the bands of fibrous tissue. These bands of fibrous tissue were wavy and in places very dense, especially in the thinner portions of the wall. Throughout the wall there were scattered collections of blood pigment, the remains of former hemorrhage.

Sections of the concretions showed them to have no definite structure and no enveloping membrane. The matrix consisted of a granular amorphous material in which the "ghosts" of cells could be seen along with irregular, short, thread-like structures, looking not unlike fine hairs. The whole mass stained uniformly with hematoxylin save a few small, round, hyaline-like bodies which stained with eosin. The "squames" were irregular in shape and showed creases

and folds.   Some of these were quite large and looked as though several squamous epithelial cells were joined together.   In one section there were seen several masses of cells with deep staining blue nuclei.   These cells formed quite large irregular islands and consisted chiefly of polynuclear leukocytes with a number of large endothelial-like cells similar to those in the cyst wall.   No relationship between these cells and the surrounding substance of the concretion could be made out.   In the outer part of the concretions the substance was more closely packed and stained more deeply.   There was, however, no evidence of a stroma or of cells forming an enveloping membrane. Sections stained by van Gieson showed no evidence of connective tissue.

Smears made from the concretions stained with Sudan showed large round fat droplets with a great deal of finely granular material also taking this stain.   Sections counterstained with hematoxylin showed the outlines of the epithelial squames.   These cells showed the same characters as those above described.

The fat contained within the concretions was semisolid at room temperature and of smeary character.   By placing a ball in a test-tube and immersing the tube in a water bath, a golden yellow liquid fat was seen to escape but the ball retained its general form save that it showed a number of crevices.   This golden yellow fat was identical in color and consistency with the oily fluid observed in the central cleft of the concretion.   A ball placed in ether lost its form and a cloudy yellowish solution was obtained, leaving, however, a considerable undissolved granular sediment.   Stained smears of this residue showed many of the "squames" as well as a great deal of amorphous débris which also stained with the hematoxylin.

Direct smears of the dermoid balls showed no evidence of cholesterin crystals, but on examination with Nicol's prism many doubly refractile bodies were seen while the presence of cholesterin was obtained by Salkowski's test.

A comparative examination of the lipoid material in ordinary dermoids and of the concretions showed the following:

Ordinary dermoid.	Dermoid concretion.
1. Material semifluid at 37° C.	1. Concretions semisolid.
2. Much hair intermixed.	2. Few hairs in concretions themselves.
3. Small granular fat particles.	3. Large fat drops.
4. Small amount of débris.	4. Much débris of cells.
5. Squames, few.	5. Squames, many.
6. Cholesterin (chemically).	6. Cholesterin (chemically).
7. Double refractile bodies present in great numbers.	7. Double refractile bodies present.
8. No inflammatory cells.	8. Inflammatory cells.

The comparative analysis of the two types of material showed that the material in the concretions differed somewhat from the ordinary dermoid contents. In other words, it would seem that the cyst in question was originally of the ordinary type and that owing to a subsequent change in its contents an unusual physical appearance was brought about. This change would seem to be due to the action of a number of factors, the chief of which was the addition of dry keratinized cells and other cell débris accompanied by a change in the character of the fatty contents of the cyst.

The presence in the wall of the cyst of a very marked inflammatory reaction and the finding of inflammatory exudate and leukocytes in sections of the dermoid balls indicates that there had been an inflammatory reaction on the inner surface of the cyst and that the exudate had become mixed with the sebaceous material. The addition of an exudate of this nature would offer substances which might easily change the nature of the fatty compounds. Particularly of note would be the enzymes liberated on dissolution of the inflammatory cells which to a greater or less extent would act upon the lipoid compounds. It is impossible to indicate the exact nature of these reactions. It is interesting, however, that a greater number of double refractile bodies were seen in the ordinary dermoid material, than in the fatty concretions of the case under discussion. With this difference in the fatty content and the addition of products of an inspissated exudate, together with the epithelial squames, the material has become dry and crumbly. The presence of the great amount of amorphous granular débris resulted from the disintegration of the desquamated cells and the cells of the exudate. The large size of the fat droplets, as compared with the small granular fat in ordinary dermoids, also indicates an alteration in the character of the lipoid material. From the appearance of the sections of the concretions, the relatively large amount of granular débris suggests that its physical properties played a very important part in the preparation of the material for the formation of the concretions.

A recent article by M. Lippert thoroughly reviews the literature concerning the occurrence of fatty concretions in dermoids together with the findings in a case which came to Schwalbe's laboratory.

The many explanations for the occurrence of these fatty concretions contain interesting points for discussion. It would appear from our findings that some authors lay too much stress upon factors which seem of relatively minor importance.

In order to explain the occurrence of these sebaceous concretions it is at once necessary to determine the change which has been

brought about in the contents of the cyst as differing from that in ordinary dermoids.

It has been the opinion of Askanazy, Olshausen, Plenz, and others that a torsion of the pedicle of the cyst with the subsequent serous effusion into the cavity of the cyst was the primary cause for the occurrence of the globular masses. Further it was suggested that a mechanical influence had been exerted upon the fat suspended in the fluid and by a kneading motion had led to the formation of the balls. In support of this contention Plenz found that it could be imitated in analogous experiments. Kermauner formed flat flakes by the addition of sulphuric acid and barium chloride to a fatty suspension. He concluded, however, that although the ball formation was not unlike a colloid precipitate, it was uncertain whether this occurrence *in vitro* was analogous to the ball formation without further evidence. In his conclusion Kermauner recognizes the uncertainty of his observation as there are reported cases where there was no fluid present in which the fat could be precipitated. Among such reported cases are those of Latsko, Mohr, and Schwalbe, while no sign of fluid was found in our cyst. In the three cases cited above there was also no evidence of torsion of the pedicle. The cases of Latsko and Schwalbe were ovarian dermoids while that of Mohr was a dermoid cyst of the floor of the mouth.

Torsion of the pedicle of the cyst is a point upon which much stress has been placed. A torsion is a mechanical obstruction to the circulation brought about by a twisting of the pedicle. The obstruction may vary in its intensity and, depending upon this, several conditions may occur, namely, edema, an inflammatory reaction or gangrene. The three conditions named would form a sequence of events following one upon the other in the presence of a severe prolonged torsion. If torsion played a part in the picture presented by our case, it would appear that it induced an acute inflammatory reaction with the pouring out of a cellular exudate into the cavity of the cyst.

Latsko, in whose case there was neither torsion of the pedicle or fluid in the cyst, believes that a physicochemical process must have occurred with the change of the character of the contents from the fluid form to the solid state. He goes still further and says that a mere mechanical forerunner can be precluded in his case as there was no fluid in which the concretions could be rolled up and broken off.

In his original article Schwalbe, in discussing the occurrence of the fatty concretions in the case recently reported by his pupil, M.

Lippert, says that an intimate mechanical mixture of the fat with epithelial scales would guarantee a holding together of the masses at body temperature.   In an analysis of the fat of the concretions he found the melting-point to be 30° C., and that of a simple dermoid between 28–30° C., both considerably under the body temperature. In the microscopical examination of the masses he found them to be made up of large fat drops and a finely granular débris mixed with a great number of epithelial scales.   He attributes the great number of epithelial scales to the fact that the cyst was completely lined by a stratified squamous epithelium showing cornification.   In the examination of the fat of the other dermoid he found a finely granular fat with a small number of epithelial scales.   The lessened amount of the scales was attributed to the fact that the cyst was not completely lined by squamous epithelium.

He found that when a concretion was placed in the incubator for twenty-four hours it still retained its form and further that when placed in boiling water the form was not changed.   In order to prove his contention that only an intimate mechanical mixture of the fat and epithelial scales was necessary for these concretions, he demonstrated their artificial formation by working together the sebaceous material of dermoids with bread crumbs.   These artificially produced concretions indicated physical properties similar to those from dermoids.

In conclusion Lippert says the primary cause of the ball formation depends upon the character of the cyst contents.   Upon this fact the whole question of the occurrence of these fatty concretions is based and it would appear that the inflammatory reaction which is evidenced in our case had something to do with the proper preparation of the contents.

Although the chemical analyses of the fat in the two dermoids examined by Schwalbe indicated a similar mixture it would appear from the microscopical examination that a physical or morphological change had occurred in the fat of the sebaceous concretions.   In the fat of the concretions there were found large fat drops in comparison to the finely granular fat in the ordinary dermoid material.   Whether this morphological difference is purely a physical one or indicates a chemical change would be hard to say unless the material were examined immediately after removal from the body, owing to the tendency to decomposition of fatty compounds on preservation. However, from the characters presented it would appear that there was some difference in the fatty material.   As stated before, Latsko was of the opinion that such a change had occurred in his case.

Rokitansky, referring to the formation of the concretions, indicated

that in addition to the presence of an exudate a rolling and tumbling movement of the cyst facilitated the formation of the masses.

The addition of a large amount of cell detritus undoubtedly makes the material dry and crumbly. Such an addition could be offered in a purulent exudate which had become inspissated, of which we have evidence in our case in the presence of an inflammatory reaction in the wall of the cyst and on its inner surface. Furthermore, inflammatory cells were found in the sections of the balls which showed that a purulent exudate had been mixed with the fat.

In our case the mixture of epithelial scales with the fat did not appear to be the prominent feature. In paraffin sections epithelial cells were seen to be widely separated by a finely granular débris and were in very small amounts compared with the large amount of débris. Some of this débris could be accounted for by the disintegration of the lining cells while the evidence of a purulent exudate in the cyst cavity would also account for much of it. The addition of such an inspissated exudate in life would be analogous to Schwalbe's experiment in which he added bread crumbs to bring the fat into a proper consistence for moulding. Then with the material in a mastic state and with the natural cohesive power of the fat these small particles would be welded together as the cyst was rolled about on its pedicle.

Since the foregoing study was completed we have had the opportunity of studying a dermoid (sebaceous) cyst of the scalp which showed a similar arrangement of its contents into small ball-like masses as above described. The specimen was removed by operation from a man of fifty-nine years by Dr. A. Stewart, Surgeon to the Mercy Hospital.

The cyst occupied the scalp in the upper anterior part of the left temporal region and consisted of a mass the size of a tangerine orange measuring 5 centimeters in diameter. The wall of the cyst was quite thin and showed a white, scaly, keratinized epithelial lining. Microscopical examination of these scaly flakes showed epithelial squames and enormous numbers of cholesterin crystals. There was no evidence of fluid in the cyst and there were no hairs present. The contents consisted of a crumbly light brown sebaceous material in which small balls varying from the size of a match head to that of a pea were mixed together with irregular pieces of a soft white material similar to that adherent to the wall. Microscopical examination of the white material in the contents showed only solid masses of cholesterin crystals. The striking feature of the contents was its dry crumbly nature and the fact that each one of the small balls was

found lying in a pocket separate from the surrounding material. These sebaceous concretions were quite rough on their surface. In this respect they were quite different from the balls described in the foregoing case. On section these balls did not contain a nucleus of any kind and, moreover, there was no evidence that the white flakes of cholesterin material ever acted as such. It is very suggestive that in this case we are dealing with the early or incomplete formation of the ball-like masses of sebaceous material. The variation in size also points to the fact that the process was incomplete at the time of operation. Only a few masses had reached the final stage of ball formation.

Microscopical examination of the cyst wall showed it to be lined by a fairly thick layer of stratified squamous epithelium surmounted by a heavy keratinized stratum. In the subepithelial tissues there was quite a marked inflammatory reaction made up chiefly of polynuclear leukocytes together with a few lymphocytes and an occasional plasma cell and eosinophile. At certain points these inflammatory cells could be seen breaking through the epithelial lining.

Microscopical examination of the contents showed enormous numbers of closely packed epithelial squames, cholesterin crystals, fine granular fat and débris. In paraffin section of the concretions, the appearance was quite similar to that described in the previous case, save for the fact that in the present instance the "squames" appeared to be more numerous and that inflammatory cells of the polynuclear type were more easily demonstrated.

I am indebted to Dr. Oskar Klotz for assistance during this study and in the preparation of the paper, and to Dr. X. O. Werder for the materials of the first case.

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